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Journal of Chromatography A, 1018 (2003) 53–62
JOURNAL OF CHROMATOGRAPHY A
www.elsevier.com/locate/chroma

Determination of antioxidant migration levels from low-density polyethylene films into food simulants☆

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Received 7 March 2003; received in revised form 4 August 2003; accepted 12 August 2003

Abstract

An analytical method for the determination of specific migration levels of phenolic antioxidants from low-density polyethylene (LDPE) into food simulant has been developed. The screening and response surface experimental designs to optimize the liquid–liquid extraction (LLE) of these antioxidants have been tested and the analyses have been carried out by reversed-phase high-performance liquid chromatography (HPLC) coupled with ultraviolet diode-array detector. The procedure developed has been applied to specific migration tests in different commercial LDPE films. The considered antioxidants have not been found upper the legislation limits although Ethanox 330 and Irgafos 168 have been found at trace level.

Keywords: Packaging materials; Antioxidants; Polyethylene; Phenolic compounds

1. Introduction

Commercial polyalkenes need the addition of suitable amounts of additives to prevent their degradation both during processing and during their lifetime, and to get best performances in their specific end-use applications [1]. If the polyalkenes are used for packaging food, these additives or their degradation products can migrate from plastics to foodstuffs during the processing or storage. So, legislation imposes specific migration limits upon individual substances with the potential to migrate from plastics to foodstuffs according to their individual toxicity [2,3].

All polyolefins contain at least one antioxidant but synergistic mixtures of primary ("long-term antioxidants") and secondary antioxidants ("processing antioxidants") are usually employed [4]. Primary antioxidants are radical scavengers or hydrogen donors or chain reaction breakers, the major molecules of primary antioxidants include hindered phenols and secondary aryl amines. Secondary antioxidants are peroxide decomposers, they are composed of organophosphites and thioesters [5].

Different procedures have been employed to study specific migration levels of antioxidants. Till et al. [6] measured the migration of the antioxidant

☆ Presented at the 2nd Meeting of the Spanish Society of Chromatography and Related Techniques, Barcelona, 26–29 November 2002.

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doi:10.1016/j.chroma.2003.08.025

2,6-di-*tert*-butyl-*p*-cresol (BHT) from high-density polyethylene (HDPE) in a variety of food and food simulants by high-performance liquid chromatography (HPLC). Garde et al. [7,8] characterized the migration of antioxidants (Irgafos 168 and Irganox 1076) from polypropylene into fatty and aqueous food simulants, aqueous simulants were fully evaporated with nitrogen at room temperature and the residues were dissolved in chloroform and analyzed by gas chromatography equipped with flame ionization detection (FID). Marque et al. [9] studied the migration of antioxidants (BHT; 2,4-di-*tert*-butylphenol (DBP), Irgafos 168, Irganox 1010, and Irganox 1076) into food fatty simulants from a five-layer material, the contact layer was polypropylene. Migration levels were determinate by ^{1}H NMR, GC, and HPLC. Berg et al. [10] developed a study of specific migration of polymer additives from polypropylene to an acid-based food simulant. They studied the antioxidants Irganox 1010 and Irgafos 168 by liquid–liquid extraction (LLE) with chloroform, concentration under a gentle stream of nitrogen and analysis by supercritical fluid chromatography (SFC) equipped with FID.

Liquid chromatography has been proved as an accurate and reproducible technique for identification and quantification analysis of antioxidants by different authors [4,9,11–24]. This paper reports a method for the determination of specific migration levels into aqueous food simulant (simulant A) of some phenolic antioxidants, Ethanox 330, Irganox 1010, Irganox 1076, BHT (butylated cresol), *tert*-butyl-hidroxyanisole (BHA), a phosphite antioxidant Irgafos 168, and its degradation product DBP in LDPE for food packaging applications. The method combines liquid–liquid extraction and HPLC. Some of these antioxidants appear in the incomplete list of additives which may be used in the manufacture of plastics materials intended to come into contact with food: Irganox 1010, Irgafos 168, and Ethanox 330 appear without specific migration level (SML) and Irganox 1076 with 6 mg kg^{-1} as SML and cresol with 12 mg kg^{-1} as SML [3].

2. Experimental

2.1. Reagents and solvents

n-Hexane, methanol, and tetrahydrofuran (THF) HPLC-gradient grade for instrumental analysis were supplied by Merck (Darmstadt, Germany); acetonitrile HPLC-gradient grade for instrumental analysis, nitric acid 60% for analysis, and sodium hydroxide (98%) for analysis were obtained from Panreac Química (Barcelona, Spain) and sodium sulfate anhydrous (≥99%) was from Fluka (Buchs, Switzerland). Water was purified on a Milli-RO system (Millipore, Bedford MA, USA).

The studied antioxidants were obtained from the following sources: butylated hydroxyanisole (BHA, mixed isomers 2,3-*tert*-butyl-4-hydroxyanisole; 2,3-*tert*-butyl-hydroquinone monomethyl ether, minimum 90%-3 isomer/9%-2-isomer) CAS No. [25013-16-5]; 2,6 di-*tert*-butyl-*p*-cresol (99%) CAS No. [128-37-0], and 1,3,5-trimethyl-2,4,6-tris(3,5-di-*tert*-butyl-4-hydroxybenzyl)benzene (Ethanox 330, 99%) CAS No. [1709-70-2] from Sigma Aldrich (Steinheim, Germany). 2,4-Bis(1,1-dimethylethyl)-phenol (DBP, ≥98%) CAS No. [96-76-4] from Fluka. Tris(2,4-di-*tert*-butylphenyl)phosphite (Irgafos 168) CAS No. [31570-04-4]; pentaerythritol tetrakis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl]propionate (Irganox 1010) CAS No. [6683-19-8], and octadecyl-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-propionate (Irganox 1076) CAS No. [2082-79-3] from Ciba (Basel, Switzerland).

Individual stock standard solutions of each antioxidant (1000 mg l^{-1}) were prepared in acetonitrile for BHA, DBP, BHT, and Irganox 1010, in a mixture of methanol-tetrahydrofuran (75:25) for Ethanox 330 and in tetrahydrofuran for Irganox 1076 and Irgafos 168.

According to Garde et al. [7,8] fully oxidized Irgafos 168 can be obtained after 24 h of dissolution in THF. Therefore, instead Irgafos 168 there will be its oxidized product because we have employed THF in stock standard solutions preparation. So, in this work, oxidized product of Irgafos 168 was analyzed.

Stock standard solutions containing all the compounds were prepared from individual standard solution (1000 mg l^{-1}) by dilution with acetonitrile.

2.2. Instrumentation and chromatographic conditions

The chromatographic experiments were carried out on a Waters 2695 (Waters, Milford, MA, USA) with a gradient pump and automatic injector. The

seven analytes were completely separated using a stainless steel column 150 mm × 3.9 mm packed with Nova-Pack C_{18} 60 Å, 4 μm particle size (Waters) maintained at 30 °C. The detection system was a model 996 UV photodiode array (Waters) and the detection wavelength was 276 nm. The mobile phase was composed of methanol and water. The eluent flow rate was 1 ml min^{-1}. Gradient elution for antioxidants consisted of a 5 min linear gradient from methanol–water (20:80) to 60% methanol, 4 min linear gradient to 100% methanol, and 8 min isocratic elution at 100% methanol. The injection volume was

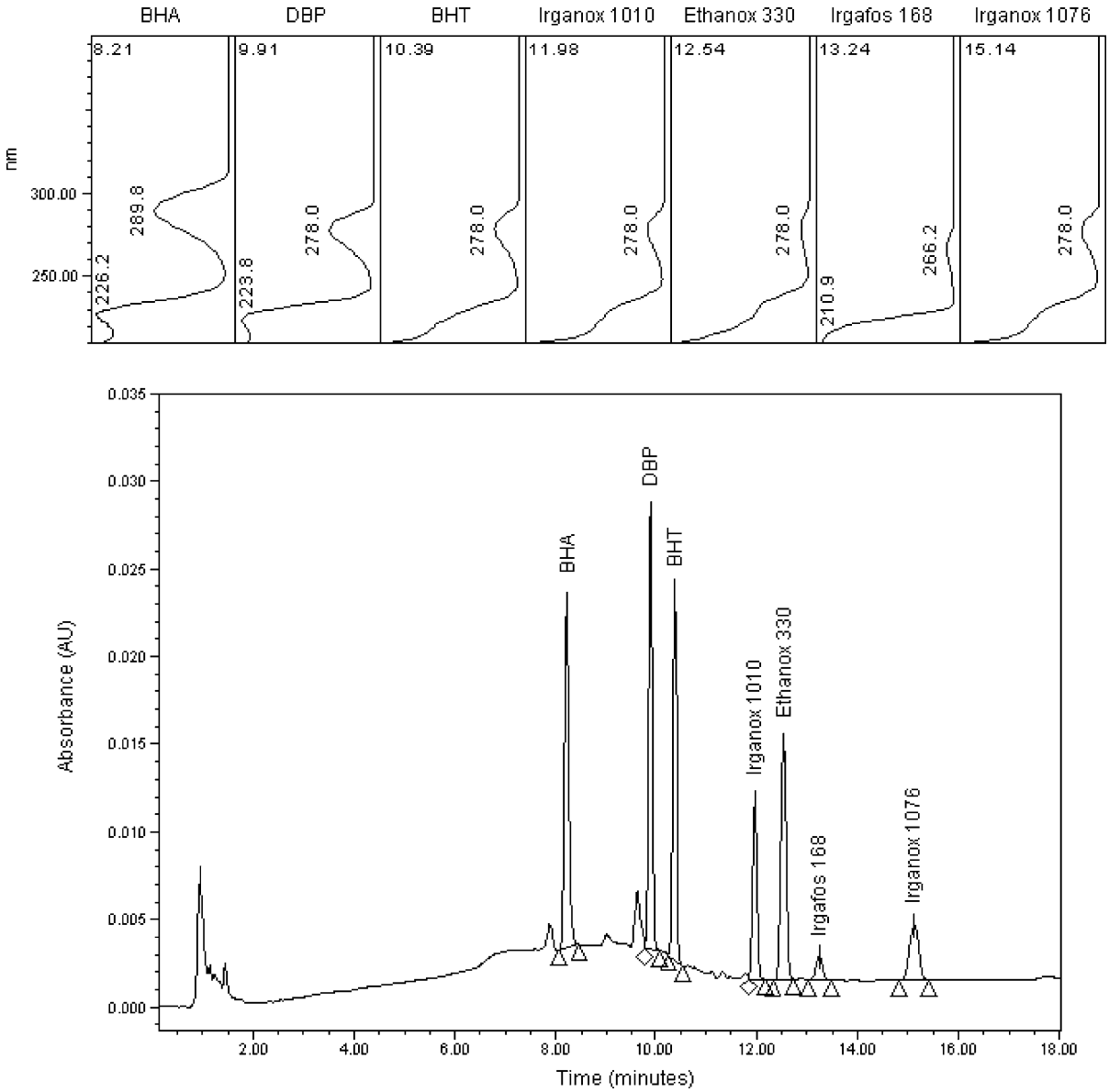

Fig. 1. HPLC chromatogram of standard antioxidants (approximately 10 mg l^{-1}), column: Nova-Pack C_{18} (30 °C), mobile phase: methanol–water (gradient elution), $\lambda = 276$ nm, and injection: 20 μl.

20 μl. HPLC chromatogram obtained under these conditions is shown in Fig. 1. The signal acquired from detector was recorded by a personal computer operated under the Millenium^{32} software V. 3.20 (Waters).

Each compound was identified by comparison of its retention time with corresponding peak in the standard solution and its UV spectrum. Quantification was carried out using a calibration plot of external standard (five points between 2.5 and 20 mg l^{-1}).

2.3. Liquid–liquid extraction

Liquid–liquid extraction was performed in a separatory funnel (250 ml). A sample volume of 100 ml of simulant A after migration test and *n*-hexane as extraction solvent were chosen. pH, *n*-hexane volume, extraction time, operator, and delay time conditions for the separation into organic and aqueous phases were studied. Aqueous samples extracted three times consecutively, the *n*-hexane extracts were dried with sodium sulphate after extraction, were combined in a pear-shaped recovery flask, and the volume was reduced until the last drop at 200 mbar and 30 °C by rotary evaporator. The drop was diluted with 1 ml of acetonitrile, and analyzed by HPLC–UV diode-array detection.

2.4. Specific migration test

The analytical method was applied to LDPE commercial samples, films for alimentary use, food-freeze bags and ice bags. Milli-RO water was used as food simulant. Single-surface exposure tests were performed using glass single face migration cells for films and food-freeze bag and ice bag filling for this last kind of samples according UNE-ENV13130-1 [25].

A temperature of 40 ± 1 °C and a time of 10 days were chosen as test conditions related to condition of use. The cell volume and contact surface were 175 ml and 1 dm^2, respectively related to the 0.6 dm^2 to 100 ml simulant ratio established by EU regulation [25]. Volume and exposure surface in article filling test is not regulated. After 10 days, food simulants were removed from the cells and bags and stored at 4 °C until analysis.

3. Results and discussion

3.1. Dissolution of extract residue

Dissolution of extract residue was studied because of weak solubility antioxidants showed in a lot of solvents. First, 20 ml of *n*-hexane were spiked with all antioxidants until 0.5 mg l^{-1} for each one and then they were evaporated using rotary evaporator. The performance of acetonitrile and tetrahydrofuran to dissolve the extract residue was compared. Recovery data obtained are shown in Table 1 and they are similar for both solvents (80–90%). The re-dissolution of studied antioxidants was even achieved for antioxidants with weak solubility (Ethanox 330, Irgafos 168, and Irganox 1076). Acetonitrile was chosen as solvent to dissolve extract residue according R.S.D. values below 10.2% in front of tetrahydrofuran R.S.D. values that show three antioxidants with recovery R.S.D. value upper 10.

3.2. Liquid–liquid extraction

Initially, four factors were selected as potentially affecting the extraction efficiency, namely: extraction time, volume of *n*-hexane, operator, and sample pH. Considering that the studied antioxidants are phenolic compounds, pH was included between the factors. Different works show that the acidification of the sample allows them better recoveries of phenolic compounds by solid-phase extraction (SPE) with different kinds of sorbents from aqueous samples [26–31] because it has been proved that the

Table 1
Effect of solvent on re-dissolution of residue after evaporation in liquid–liquid extraction

	Redissolution in tetrahydrofuran		Redissolution in acetonitrile	
	Recovery (%)	R.S.D. (%)	Recovery (%)	R.S.D. (%)
BHA	85	5.3	86	7.5
DBP	85	6.6	86	8.7
BHT	76	13	82	9.1
Irganox 1010	83	6.4	88	8.2
Ethanox 330	83	5.2	86	7.1
Irgafos 168	88	10	86	10
Irganox 1076	91	12	86	7.0

Table 2
Factor levels in the designs for antioxidants LLE optimization

Factors (units)	(−)	(+)
Plackett–Burman 2^{6*} 3/16		
Extraction time (s)	20	300
Extraction volume (ml)	15	30
pH	2	8
Operator	−1	+1
Central composite design 2^3 + star		
Extraction time (s)	20	300
Delay time (min)	2	10
pH	2	7

acidification of the sample avoids the phenols desprotonation.

To screen the relative influence of these factors and their possible interactions in the experimental domain, a factorial design Plackett–Burman 2^{6*} 3/16 resolution III was chosen. The effects of the selected four factors were studied in 12 runs. The values corresponding to the upper (+) and lower (−) levels taken by each variable in this design are listed in Table 2.

Hundred milliliter of water Milli-RO spiked with antioxidants until 0.1 mg l^{-1} were employed for all analysis. Liquid–liquid extraction was performed with pH, volume, extraction time, and operator conditions fixed in the design matrix for each run (Table 3) and delay time for the separation into organic and aqueous phases was 8 min. The desired pH was obtained by addition of nitric acid 1 M.

Data analysis was performed with the statistical package Statgraphics Plus for Windows V. 4.0. The analysis of these results showed that no significant interactions between factors were apparent. *P*-value of the considered factors for each antioxidant is shown in Table 4 and Fig. 2, and the factors that have a significant effect on recovery are: pH and extraction time. pH was the factor with greatest effect, in fact the only statistically significant factor for all compounds (Table 4) and the recoveries increased when pH decreased (Fig. 2). Extraction time produced significant effect for BHT and DBP (Table 4) but percentage of recovery decreased when extraction time increased (Fig. 2), opposite it was expected. This same effect was observed for BHA, although it decreased less. The different behavior of these three antioxidants can be related to their lower molecular mass and upper polarity than others studied antioxidants.

So, a second experimental design was planned to evaluate the optimum for each significant factor. Volume of *n*-hexane (15–30 ml) in the first design produced significant effect only for BHA (Table 4), the recovery of BHA increased when volume increased (Fig. 2), so the volume was fixed in 20 ml, in three fractions of 10, 5, and 5 ml, respectively. Operator produced significant effect only for BHT therefore, was not considered in the second experimental design.

Table 3
Design matrix and recoveries in the Plackett–Burman 2^{6*} 3/16

Run	Variables				Recovery (%)						
	pH	Hexane volume for each fraction (ml)[a]	Extraction time for each fraction (s)	Operator	BHA	DBP	BHT	IGN 1010	E 330	IGF 168	IGN 1076
1	7	5	300	−1	77	77	71	21	34	35	40
2	7	10	20	1	80	83	69	23	34	35	33
3	2	10	300	−1	87	85	77	70	78	77	79
4	7	5	300	1	64	62	49	15	20	13	13
5	7	10	20	1	84	82	76	29	28	30	32
6	7	10	300	−1	81	80	79	22	38	39	41
7	2	10	300	1	85	83	71	65	71	71	70
8	2	5	300	1	82	82	68	66	81	80	84
9	2	5	20	1	79	84	76	36	61	62	68
10	7	5	20	−1	80	84	71	41	48	52	52
11	2	10	20	−1	92	89	88	66	70	72	75
12	2	5	20	−1	86	87	90	58	66	67	73

[a] Aqueous sample was extracted three times consecutively with hexane volume indicated for each fraction.

Table 4
P-value of the considered factors for each antioxidant Plackett–Burman 2^{6*} 3/16 ($\alpha = 0.05$)

	pH	Volume	Extraction time	Operator	Factor *E*	Factor *F*
BHA	0.0110	0.0178	0.0832	0.0630	0.5200	0.2649
DBP	0.0379	0.1628	0.0392	0.1327	0.3632	0.3831
BHT	0.0497	0.1659	0.0550	0.0270	0.7068	0.4191
Irganox 1010	0.0056	0.4504	0.8896	0.3653	0.7598	0.6589
Ethanox 330	0.0009	0.8222	0.6516	0.2636	0.3058	0.6766
Irgafos 168	0.0018	0.7029	0.9493	0.2190	0.2872	0.6918
Irganox 1076	0.0009	0.9910	0.8829	0.1308	0.1833	0.5662

If *P*-value <0.05, the considered factor is statistically significant.

Instead, a new variable was considered, delay time for the separation into organic and aqueous phases to reduce emulsions that could affect the recoveries. Therefore, extraction time, pH, and delay time for the separation into two phases were considered in the second experimental design by applying a central composite design $2\hat{3}$ + star, which studied the effects of these three factors in 16 runs no randomized. Table 2 shows the upper (+) and the lower (−) values taken by each variable in this second design. In the same way, that in first experimental design liquid–liquid extraction conditions were optimized using a constant sample volume of 100 ml and concentration 0.1 mg l^{-1} in all the design experiment.

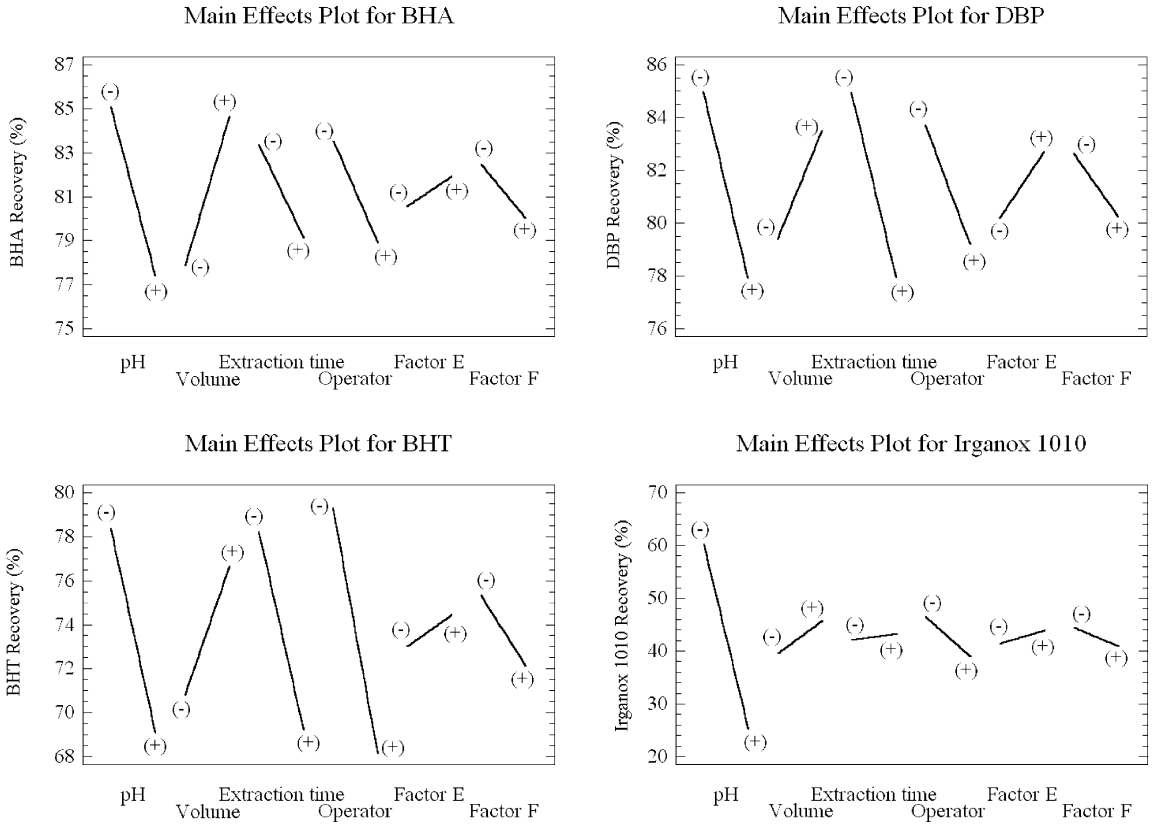

Fig. 2. Main effects plot for each component Plackett–Burman 2^{6*} 3/16.

Table 5
Design matrix and recoveries in the central composite design 2^3 + star

Run	Variables				Recovery (%)					
	pH	Extraction time for each fraction (s)[a]	Delay time for each fraction (min)	BHA	DBP	BHT	IGN 1010	E 330	IGF 168	IGN 1076
1	4.5	160	6	82	78	49	39	41	44	43
2	2.0	20	2	84	87	68	66	79	82	79
3	7.0	20	2	86	85	68	29	30	37	34
4	2.0	300	2	82	85	65	79	81	84	77
5	7.0	300	2	63	63	35	15	36	41	39
6	2.0	20	10	77	85	68	38	60	57	56
7	7.0	20	10	82	77	45	27	38	41	41
8	2.0	300	10	88	89	67	69	77	85	77
9	7.0	300	10	78	77	30	32	43	48	46
10	0.3	160	6	77	85	51	64	62	72	65
11	8.7	160	6	81	82	44	29	35	40	38
12	4.5	0.0	6	20	32	24	22	26	28	26
13	4.5	395	6	92	89	71	62	73	79	76
14	4.5	160	0	80	79	55	30	36	47	39
15	4.5	160	13	92	89	77	60	69	83	68
16	4.5	160	6	87	87	64	43	47	51	51

[a] Aqueous sample was extracted three times consecutively with hexane volume indicated for each fraction.

Data analysis was also performed by means of the statistical package Statgraphics Plus for Windows V. 4.0 as the first design. Recoveries of antioxidants for every run are shown in Table 5. The pH and extraction time produced significant effect for Ethanox 330, Irgafos 168, Irganox 1010, and Irganox 1076 while delay time did not produce significant effect. No significant interactions between factors were detected. Fig. 3 shows the estimated response surface for each antioxidant. The lowest pH and the highest extraction time produced the best response. Although delay time did not show significant effect the highest delay time produced the best response except for Irganox 1010 and Ethanox 330 that were approximately constant.

Therefore, according to results, the best conditions for the LLE would be: the lowest pH, high extraction time, and high delay time.

3.3. Finally LLE conditions

The following optimal values were adopted for the extraction of considered antioxidants from water samples: pH: 0.5, volume: 20 ml (1 × 10 ml, 2 × 5 ml), extraction time: 6 min, and delay time: 10 min.

Table 6 shows the results of repeatability study, and detection (DL) and quantification (QL) limits for the optimized LLE–HPLC–UV analytical method to determine the seven antioxidants from water samples. The developed method allows obtaining recoveries between 70 and 88% for every antioxidant except for Irganox 1010 with acceptable R.S.D. values within 3.4–13%. The worst results were obtained for Irganox 1010 that shows a recovery of 66% with R.S.D. of 15%. The method enables to determine additive concentrations as low as 16–30 $\mu g\,l^{-1}$ in 100 ml of aqueous simulant.

Table 6
Repeatability of the LLE–HPLC–UV analytical method ($n = 6$) for an aqueous sample of 100 ml spiked until 0.1 $mg\,l^{-1}$, and detection (DL) and quantification limits (QL) for the method

	Recovery (%)	R.S.D.	*x*DL ($\mu g\,l^{-1}$)	*x*QL ($\mu g\,l^{-1}$)
BHA	88	4.3	6.5	22
DBP	88	3.4	4.8	16
BHT	70	8.7	5.6	19
Irganox 1010	66	15	6.0	20
Ethanox 330	71	7.1	4.3	19
Irgafos 168	76	8.5	8.8	30
Irganox 1076	71	13	7.6	25

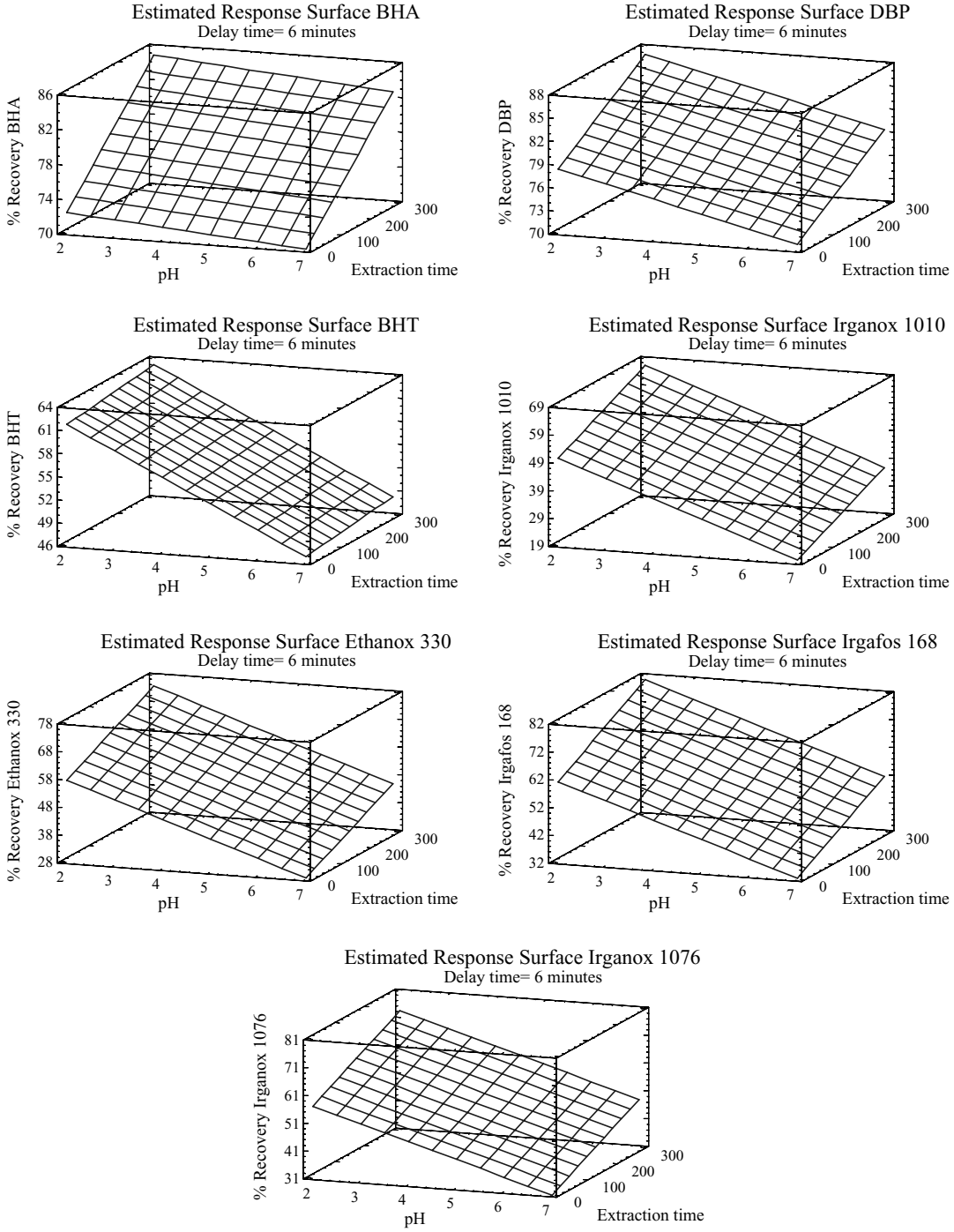

Fig. 3. Response surface for each component central composite design 2^3 + star.

Table 7
Detection (DL) and quantification (QL) limits of the LLE–HPLC–UV analytical method calculated according the exposure surface/simulant volume rate

	Cells ($\mu g\,dm^{-2}$)		Bags I ($\mu g\,dm^{-2}$)		Bags II ($\mu g\,dm^{-2}$)	
	DL	QL	DL	QL	DL	QL
BHA	1.13	3.77	0.22	0.72	0.24	0.80
DBP	0.84	2.79	0.16	0.54	0.18	0.60
BHT	0.98	3.26	0.19	0.62	0.21	0.70
Irganox 1010	1.05	3.51	0.20	0.67	0.22	0.75
Ethanox 330	0.75	3.37	0.14	0.64	0.16	0.72
Irgafos 168	1.55	5.17	0.30	0.99	0.33	1.1
Irganox 1076	1.32	4.41	0.25	0.84	0.28	0.94

Table 8
Results of specific migration tests from LDPE samples

	Cells ($\mu g\,dm^{-2}$)					Ice bags ($\mu g\,dm^{-2}$)	
	F I	F II	F III	F IV	Freeze bags	B I	B II
BHA	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
DBP	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
BHT	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Irganox 1010	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Ethanox 330	D	N.D.	N.D.	N.D.	D	N.D.	N.D.
Irgafos 168	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Irganox 1076	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.

D: detected (>DL and <QL); N.D.: not detected (<DL). Results mean of three replicates.

3.4. Specific migration tests

Detection and quantification limits of this method were rewritten according surface to simulant volume ratio (Table 7) for considered antioxidants in each kind of test with the aim of evaluating the specific migration levels of the antioxidants in aqueous simulant [25], and the results are shown in Table 8.

After migration test, food simulant samples were analyzed by performed LLE–HPLC–UV diode-array analytical method. Only Ethanox 330 and Irgafos 168 were detected in the samples. These antioxidants were below specific migration levels established by European legislation (6 mg kg^{-1} or 1 mg dm^{-2} for Irganox 1076, and 12 mg kg^{-1} or 2 mg dm^{-2} for cresols).

4. Conclusions

The following conclusions can be drawn from the present study:

(1) Evaporation by rotary evaporator was proved to be an acceptable technique to preconcentrate antioxidants without high losses.
(2) pH produced significant effect in the LLE of considered antioxidant, specialty with Ethanox 330, Irgafos 168, Irganox 1010, and Irganox 1076.
(3) Optimal conditions of LLE according to the full-factorial experimental design permitted to obtain good recoveries for all considered antioxidants from aqueous matrix with good accuracy.
(4) Specific migration test of commercial films showed that there were not considered antioxidant migration upper SML in simulant A. Irgafos 168 and Ethanox 330 could be detected.

Acknowledgements

This research has been supported by Xunta de Galicia Govern PGIDIT02PXIA17201AF (Autonomic Community Government).

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