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Analysis method

Determination of di(2-ethylhexyl) phthalate migration from toys into artificial sweat by gas chromatography mass spectrometry after activated carbon enrichment

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ABSTRACT

The determination of di(2-ethylhexyl) phthalate migration was achieved in artificial sweat using gas chromatography mass spectrometry following activated carbon enrichment of samples. Response surface methodology (RSM) was used to optimise the conditions for maximum recovery and to understand the significance and interaction of the factors affecting the recovery of di(2-ethylhexyl) phthalate. The best compromise of analytical conditions for the simultaneous determination of analyte from spiked artificial sweat was found to be: pH (3.1), activated carbon amount (1.4 g L^{-1}), adsorption time (55 min) and elution solvent (chloroform). These conditions were applied to study the migration of di(2-ethylhexyl) phthalate from different children's toys into artificial sweat. The detection limit of the method was 13.8 μg L^{-1}, while the relative standard deviation (%) value for the analysis of 100 μg L^{-1} of the analyte was below 3.7% ($n = 5$).

1. Introduction

Phthalate acid esters (PAEs), commonly known as phthalates, are added to plastics to make them soft and flexible, to cosmetics as a vehicle for fragrance, and to many other daily products, such as building materials, medical devices and children's toys. PAEs increase the flexibility of plastics only through weak secondary molecular interactions with polymer chains. These compounds are not covalently bound to the vinyl polymer matrix and can, therefore, be released fairly easily from these products [1]. Di(2-ethylhexyl) phthalate (DEHP) is one of the most important representatives of this compound class. DEHP is colorless, odourless and of high thermal stability. The chemical stability is, however, low. DEHP is easily eluted from poly(vinyl chloride) (PVC) products into not only foods but also body fluids that come into contact with the plastic, and the migrated DEHP is directly and/or indirectly introduced into the human body [2]. The migration of PAEs from some products, especially toys and childcare products, has received considerable attention in recent years [3,4] because of their possible roles as carcinogens, endocrine disruptor, reproductive and developmental toxicants to infants and pregnant women [5–9]. The exposure of children to PAEs could occur by ingestion, by dermal contact or both. The widespread use has lead to a significant exposure of humans to phthalates via food and environmental contact. In spite of the long time usage of phthalates in toys, there is not any literature concerning migration of phthalate from toys via sweat. Taking into account all of these considerations, the development of sensitive and reliable analytical methods is necessary to analyze not only the content of PAEs in these materials but also the efficiency of their migration from plastic toys into artificial sweat.

The assertion that phthalates are absorbed into the circulation through human skin is physiologically plausible and is supported by a limited number of human and animal studies. The structure of PAEs largely determines their

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percutaneous absorption, which depends on the alkyl side chain and decreases with increasing chain length, the number of branching and degree of lipophilicity [10–13]. However, the mechanism explaining differential rates of uptake is not agreed upon. In the context of EU risk assessments for DEHP (ECB 2008) and based on in vitro and in vivo data for humans, the percutaneous absorption of DEHP was estimated to be 5%, of the dermal dose at the most (worst case) [14].

Several methods for PAEs determination at very low concentrations in different matrices are found in the literature (water [15–18], food [19–21], biological samples [22–24], toys [25,26], cosmetics [27], etc.). Different sample treatments, extraction and preconcentration steps such as liquid–liquid extraction (LLE) [16,18], solid phase extraction (SPE) [19], solid phase microextraction (SPME) [20,28], stir bar sorptive extraction (SBSE) [15] and thermal desorption [17] have been used before the instrumental analysis to determine these compounds in these types of samples. In recent years, some authors have also focused their research to study the migration of phthalates from different matrices to body fluids. Bouma and Schakel applied a "Head over Heels" agitation method to determine migration of DEHP into saliva using high performance liquid chromatography (HPLC) [29]. Earls et al. [30] studied two methods for the determination of the migration of phthalates into saliva. They are based on linear horizontal agitation, and have been validated by interlaboratory trial. In our early study, the migration of some phthalates from toys to artificial saliva was determined by gas chromatography-mass spectrometry (GC-MS) after activated carbon enrichment [31]. However, there is not any literature about the migration of these compounds from toys into sweat.

Adsorption is one of the most extensively used technologies to remove and recover organic contaminants from contaminated water, with activated carbon being the most conventional adsorbent in industrial and laboratory scales. Due to the low solubility and highly hydrophobic character of PAEs, activated carbon would be an effective and reliable adsorbent for their removal from the aqueous phase. Activated carbon has been primarily utilized for the enrichment of elements from different matrices after the addition of complexing agents [32,33], but activated carbon has not been used for the determination of PAEs in sweat. Only a few studies have reported the use of an adsorption process for phthalate removal from water by activated carbon in the form of granules, powder or fiber [34–36].

Central composite design is an experimental design, useful in response surface methodology, for the optimisation of parameters with a limited number of experiments. This type of approach using screening and optimisation design steps has been applied in the determination of cadmium and lead levels in PVC samples by AAS [37] and the levels of two phthalates and five polycyclic musks in water by GC-MS after dispersive liquid–liquid microextraction [18].

The aim of our study was to develop an analytical procedure that is useful for the study of DEHP migration from plastic toys into artificial sweat using GC-MS following enrichment of the analyte with activated carbon. To obtain the best experimental conditions for the adsorption process, including pH, adsorption time and the amount of adsorbent, a central composite design experiment was performed. The optimized method was applied to study the migration of DEHP from different children's toys into artificial sweat.

2. Experimental

2.1. Apparatus

Analysis was carried out using an Agilent 7890A GC gas chromatograph equipped with a flow modulator (Agilent G3180 CFT Modulator). The effluent from the column is split to the flame ionization detector (FID) and the mass spectrometry (MSD) detector (5975 C inert XL MSD, Agilent Technologies, Palo Alto, CA). A deactivated splitter (Agilent Technologies) was used. Two parallel deactivated fused silica capillaries were connected to the splitter with the approximate split ratio of 2:1 (MS: FID). An HP-5 ms fused-silica capillary column 30 m $\times$ 0.25 i.d., with 0.25 mm film thickness was employed. The GC oven temperature was held at 70 °C for 2 min, then increased to 230 °C at a rate of 20 °C min^{-1} and held at that temperature for 5 min. The detector temperature was 230 °C with a carrier gas (helium) at a flow rate of 1 mL min^{-1}. The injector temperature was set at 280 °C. Positive electron ionization (EI) mode at 70 eV was used with a scanning rate of 3.94 scans/sec over the mass range of 40–400 amu. The MSD transfer line temperature was set at 280 °C. Selective ion monitoring acquisition mode was used for measurement collection. The ions used for quantifying the DEHP were m/z 113, 149, 167 and 279, respectively.

A Mettler Toledo pH meter (Mettler-Toledo AG, Schwerzenbach, Switzerland) was used for pH adjustment of sweat samples. Stirring was performed using Variomag Poly multipoint 15 magnetic stirrers (Thermo Scientific, Langenselbold, Germany). In vitro sweat agitation was achieved by an orbital shaker equipped with an incubator system (Heidolph Instruments, GmbH &Co. KG, Schwabach, Germany). Ultrasonic extraction was performed using an Elma Ultrasonic LC 30 H model ultrasonic bath (Germany).

2.2. Reagents

All solvents used were of analytical reagent grade. The studied compound was di-2-ethylhexyl- (DEHP) phthalate ester. A multi-compound standard (Dr. Ehrenstorfer GmbH, phthalate ester mix 1, 2000 ng μL^{-1} in methanol, Ausburg, Germany) was used for GC-MS calibration. The internal standard, benzoic acid-benzyl ester, was purchased from Dr. Ehrenstorfer (Dr. Ehrenstorfer GmbH, benzoic acid-benzyl ester, 5000 ng μL^{-1} in n-hexane, Ausburg, Germany).

Artificial sweat was prepared by dissolving 5.0 g of NaCl, 1.0 g of urea and 1.0 g of lactic acid (analytical-reagent grade, Merck) in 1 L of water and the solution pH was adjusted to 6.5 $\pm$ 0.1 with 1% NH_3 (DIN V 53160-2). Activated carbon (Sigma C-5385, Sigma Chemical Co, St. Louis, U.S.A) for adsorption experiments was in powder form. Millipore glass fiber prefilters (APFF02500) were used for the activated carbon filtration step (Millipore, County Cork, Ireland).

2.3. Adsorption of DEHP on activated carbon

The GC-MS experiments were carried out in batch mode. A volume of 50 μL of DEHP standard was spiked into 50 mL of the sweat solution to obtain an initial concentration of 2 mg L^{-1}, and the pH was adjusted by adding NaOH or HCl. The weighed portions (0.008–0.093 g) of activated carbon were then immersed in 50 mL portions of the solution. These samples were maintained under magnetic stirring between 10 and 110 min at 250 rpm and ambient temperature. The suspensions were filtered through a 25 mm diameter glass fiber prefilter using a vacuum pump, and the filters were dried in an oven at 70 °C for 15 min. Then, the filters were sonicated with chloroform using an ultrasonic bath for 15 min, 20.0 μL of benzoic acid-benzyl ester (internal standard) was rapidly spiked and the final solutions were injected into the GC-MS.

2.4. Experimental design

A five-level three-factor central composite design was employed in this study, requiring 20 experiments to analyze the adsorption parameters. The axial (or star) points were fixed according to the rotatability conditions. The three parameters and their low, central, high and star levels were as follows: pH (0.7–2.0–4.0–6.0–7.4), activated carbon amount (0.15–0.5–1.0–1.5–1.85 g L^{-1}), and adsorption time (10–30–60–90–110 min). The experimental and predicted data in terms of DEHP recoveries are shown in Table 1.

A second-order polynomial Eq. (1) that includes all interaction terms was used to calculate the predicted response:

$$y = b_0 + \sum_{i=1}^{3} b_i x_i + \sum_{i=1}^{3} b_{ii} x_i^2 + \sum_{i=j}^{2} \sum_{j=i+1}^{3} b_{ij} x_{ij} \quad (1)$$

where y is the recovery, b_0 is the offset term, b_i is the linear effect, b_{ii} is the squared effect, b_{ij} is the interaction effect and x_i is the independent variable.

The data were analyzed using Design Expert (version 7.1.4), and the coefficients were interpreted using the F-test. Two main analytical steps, analysis of variance (ANOVA) and regression analysis, were performed to establish the optimum conditions for the adsorption parameters.

2.5. Migration studies of DEHP from toys into sweat

The toys containing DEHP as plasticizers were punched over a 3 cm diameter; the total surface area was approximately 14.2 cm^2. The samples were horizontally agitated at 200 rpm (rotation stroke length of 10 mm) in 100 mL glass Erlenmeyer flasks containing 50 mL of artificial sweat on a rotary shaker in an incubator at 40 °C for 120 min. The adsorption procedure on activated carbon was then carried out under the optimum conditions.

3. Results and discussion

3.1. Optimisation of adsorption process

The main objective of this work was to develop and evaluate a statistical approach to better understand the relationships between the parameters of DEHP adsorption onto activated carbon. Optimisation of the adsorption parameters was performed using a central composite design (CCD) procedure. Twenty experiments were required in this design using five central points, and the experiments were performed randomly. In all of the experiments, 50 μL of the standard DEHP solution was spiked into 50 mL of artificial sweat, and the CCD was performed. Recovery values, which are expressed as %R, were used as the response for DEHP. The coded values and the experimental and predicted DEHP recoveries are given in Table 1, and the experimental domain is shown in Table 2.

The effects of each factor and each factor's interactions were calculated using Design Expert (version 7.1.4). Fitting the data with various models and the subsequent analysis

Table 1
Central composite design of factors with coded values and recoveries.

Exp.	pH, X_1	Factors	Adsorption time (min) X_3	DEHP recoveries (%R)	
		Activated Carbon Amount (g^{-1} L), X_2		Experimental %DEHP	Predicted %DEHP
1	−1	−1	−1	51	52
2	1	−1	−1	52	54
3	−1	1	−1	79	81
4	1	1	−1	51	61
5	−1	−1	1	52	52
6	1	−1	1	50	56
7	−1	1	1	67	73
8	1	1	1	47	55
9	−1.682	0	0	92	91
10	1.682	0	0	89	78
11	0	−1.682	0	66	65
12	0	1.682	0	100	89
13	0	0	−1.682	24	19
14	0	0	1.682	22	15
15	0	0	0	51	42
16	0	0	0	45	42
17	0	0	0	40	42
18	0	0	0	38	42
19	0	0	0	37	42
20	0	0	0	40	42

Table 2
Range of coded and actual values for central composite design.

Factors	Levels			Star points ($\alpha = 1682$)	
	Low (−1)	Central (0)	High (+1)	+α	−α
X_1 (pH)	2.0	4.0	6.0	7.4	0.7
X_2 (Activated Carbon Amount, g^{-1} L)	0.50	1.00	1.50	1.85	0.15
X_3 (Adsorption time, min)	30	60	90	110	10

of variance (ANOVA) showed that recoveries of DEHP were most suitably described with a quadratic polynomial model. The quadratic polynomial equations with significant terms from Design Expert are given in Table 3.

The quadratic polynomial model was highly significant and was sufficient to represent the actual relationship between the response and the significant parameters with very low *p*-values (0.0002) according to the ANOVA (Table 4). The coefficient of determination (R^2) value (0.9182) indicates a satisfactory relationship between the experimental data and the fitted model.

The effects of the adsorption parameters such as the pH, the activated carbon amount and the adsorption time on the recovery were investigated. The *p*-values indicate the significance of the coefficients. A value of Prob > F less than 0.05 indicates that the model terms are significant, x_2 (AC amount), x_1^2 (pH), x_2^2 (AC amount), and x_3^2 (time) were the most significant parameters (Prob > F less than 0.05) for DEHP adsorption onto activated carbon (Table 4). DEHP recovery was found to be dependent on the sweat pH, and the uptake was observed to be greater in acidic media. The adsorption phenomena of the PAEs can be explained on the basis of hydrophobic and dispersion effects [35]. In acidic media, the protonation of surface functional groups could form hydrogen bonds with the oxygen atoms of the ester groups, or adsorption can occur due to a strong specific interaction between the aromatic rings and the carbon surface [36]. Optimum adsorption time could also depend on competitive hydrophobic interactions, solubility, molecular weight and the substituent group of the PAE. The octanol–water partition coefficient (*Kow*) has been used as an indicator of hydrophobicity and of the potential for bioaccumulation of organic compound in the environment. The wide range of values of water solubility (0.0006–1.0 mg L^{-1}) and the octanol–water partition coefficient (log *Kow*; 4.20–8.90) for DEHP suggest the experimental difficulty of analyzing this compound [1].

The relationship between the adsorption parameters and the DEHP recovery was investigated using contour plots. Fig. 1 shows the effects of pH, activated carbon amount and their mutual interaction on the recovery of DEHP. An activated carbon (AC) amount of 0.08 (g) and pH of 2.3 (mL) led to the maximum recovery (100%). The effects of pH, the adsorption time and their mutual interaction on the DEHP recovery are illustrated in Fig. 2. A low pH (<2.3) increased the recovery (100%). Fig. 3 presents the effects of the AC amount and the adsorption time on the DEHP recovery. An increase in this recovery was observed with increasing AC amount. Using the model, the optimum DEHP recovery within the experimental region was determined to require pH of 2.2, 0.085 g/50 mL of AC, and 55 min adsorption time. The percentage of sorption of DEHP was found to be 92% in optimum conditions.

Table 3
The quadratic polynomial equation of recovery (%R).

	A semi-empirical equation
DEHP	$\%R = 42.18 + 7.04\,x_2 + 14.92\,x_1^2 + 12.27\,x_2^2 - 8.94\,x_3^2$

3.2. Analytical figures of merit

Quality factors, including the limit of detection (LOD), linear range, linearity (R^2) and repeatability, were investigated to evaluate the analytical performance of the proposed method under the optimal conditions. The obtained values for the described quality factors are presented in Table 5. Linearity of the calibration curve was observed in the range of 0.1–1 mg L^{-1} with correlation coefficient (R^2) value of 0.992. Inter-day precision tests ($n = 5$) were carried out by extracting a spiked sweat sample at 100 μg L^{-1}. The relative standard deviation (RSD %) was 3.7%, which indicates good method precision. The limit of detection (LOD) based on a signal-to-noise ratio (S/N) ≥ 3, 13.8 μg L^{-1} for DEHP. This LOD value of DEHP is lower than the 25 μg L^{-1} value obtained working with ultrasonic and solid phase extraction using Florisil cartridge and GC-FID determination [19]. Earls et al. (2003) [30] have reported the application of LLE in conjunction

Table 4
Analysis of variance for the fitted quadratic polynomial model for adsorption parameters for DEHP.

Source	Sum of squares	Degree of freedom	Mean square	F-value	*p*-value (Prob > F)
Model	8040.08	9	893.34	12.47	0.0002
pH (x_1)	213.88	1	213.88	2.99	0.1147
AC Amount (x_2)	677.37	1	677.37	9.45	0.0117[a]
Time (x_3)	30.36	1	30.36	0.42	0.5297
x_1x_2	276.12	1	276.12	3.85	0.0780
x_1x_3	3.13	1	3.13	0.044	0.8388
x_2x_3	28.13	1	28.13	0.39	0.5450
x_1^2	3210.18	1	3210.18	44.81	< 0.0001[a]
x_2^2	2170.83	1	2170.83	30.30	0.0003[a]
x_3^2	1151.77	1	1151.77	16.08	0.0025[a]
Residual	716.47	10	71.65		
Lack of Fit	577.64	5	115.53	4.16	0.0719
Pure Error	138.83	5	27.77		
Cor Total	8756.55	19			
R^2=0.9182					

[a] Significant at "Prob > F" less than 0.05.

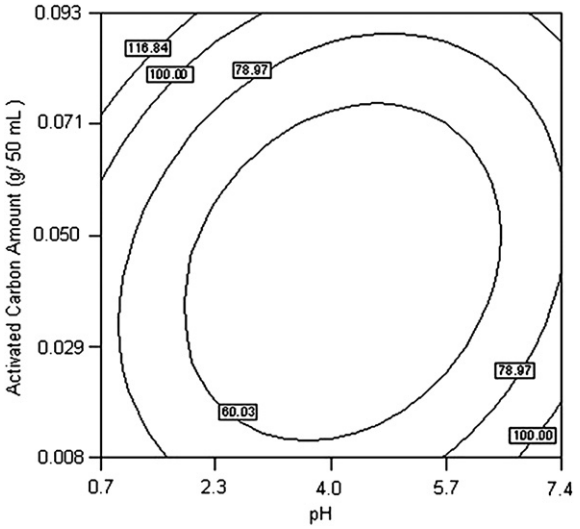

Fig. 1. Contour plot of the combined effects of pH and activated carbon amount on the recovery of DEHP.

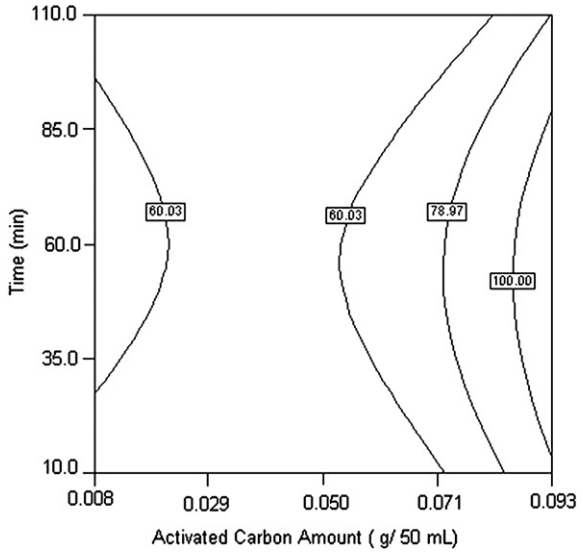

Fig. 3. Contour plot of the combined effects of activated carbon amount and time on the recovery of DEHP.

with GC–MS, for the determination of the migration of phthalate plasticisers from polyvinyl chloride toys and childcare articles. The target analytes used were different in comparison to our study, with the exception of DEHP. According to Earls et al. (2003) [30], LODs were in the range of 0.1–3.5 μg L^{-1}, while recovery values varied in the range of 86–90%. It should be mentioned that for DEHP, recovery values (88%) and LODs (0.1 μg L^{-1}) are slightly worse compared to our study (92% and 13.8 μg L^{-1}, respectively). A higher RSD% values were found by Chen et al. [20] who applied headspace solid-phase microextraction followed by GC-FID for the determination of PAEs in beverages.

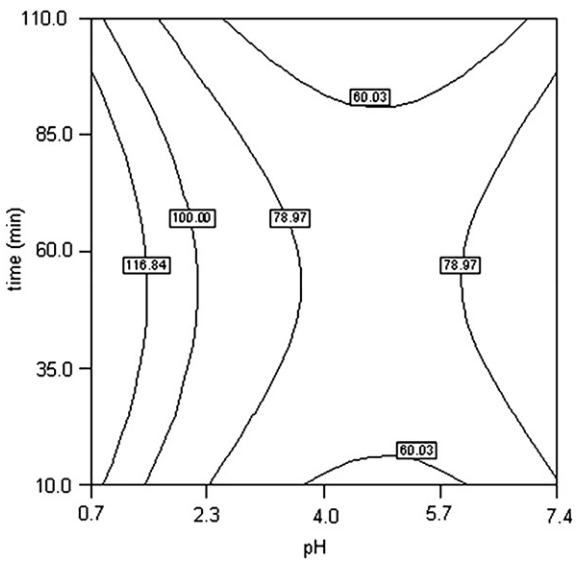

Fig. 2. Contour plot of the combined effects of pH and time on the recovery of DEHP.

3.3. Determination of DEHP migration into sweat from toys

A horizontal agitation method was utilized for 2 h at 40 °C to extract DEHP into the simulated sweat. The optimized method was applied to the analysis of different kinds of toys, and DEHP was the sole analyte detected in these samples; the results are presented in Table 6. The total DEHP concentration of toys samples was determined by ultrasonic extraction method, described in our early study [31]. The migration and standard deviations were based on the migration results from three test specimens punched out of the toy sample. In the present study, it was observed that all of the toys had DEHP release values higher than our previous work [31]. This observation can be explained by the presence of lactic acid (1 g L^{-1}) and urea (1 g L^{-1}) in artificial sweat solution, which increase the water solubility of DEHP. Previous reports in the literature demonstrate that the water solubility of DEHP can be significantly increased by humic acid [38]. Carboxyl groups of humic and lactic acids might demonstrate similar effect onto DEHP solubility.

The DEHP release depends not only on the plasticizer content in the plastic but also on other factors such as surface roughness, coating type and thickness [29]. It is very important that the exposure amount be exactly determined to conduct a risk assessment of the effect of DEHP on human health. After DEHP migration into sweat, it could be absorbed into the circulation through human skin.

Table 5
Analytical performance of the proposed method.

Name	Linear range (mg L^{-1})	R^2	LOD[a] (μg L^{-1})	RSD, %[b] ($n = 5$)
DEHP	0.10–1.0	0.992	13.8	3.7

[a] Limit of detection for S/N = 3.
[b] Relative standard deviation at the concentration of 100 μg L^{-1} of DEHP.

Table 6
Migration of DEHP into artificial sweat and DEHP content of toys ($n = 3$).

Sample	Sample mass (g)	DEHP released (μg)	DEHP released rate (μg/10 cm^2/h)	[DEHP] in toys (% w w^{-1})
Toy 1	1.30 ± 0.18	65.02 ± 9.14	16.59 ± 2.33	33.9 ± 1.4
Toy 2	1.00 ± 0.13	n.d	n.d.	0.051 ± 0.004
Toy 3	1.38 ± 0.24	129.91 ± 47.48	33.14 ± 12.11	37.9 ± 2.0

The percutaneous absorption of DEHP was estimated to be at most 5% of the dermal dose [13]. In addition, the concentration and rate of PAE release are dependent on content of sweat and conditions of migration using different agitation methods.

4. Conclusions

Despite the recent public and scientific interest in the potential human health effects of phthalates, routes of human exposure to phthalates have not been adequately characterized. Potential routes include dietary ingestion of phthalate-containing foods, inhalation of indoor and outdoor air, and dermal exposure through the use of personal care products and toys that contain phthalates. The activated carbon enrichment method has been shown to be a useful approach in the determination of the migration of phthalates into sweat. This study demonstrated the utility of experimental design optimisation of the adsorption conditions in a reasonable number of experiments. A second-order model was obtained to describe the relationship between the recovery of DEHP and pH, AC amount and adsorption time. The results indicated that pH, the amount of activated carbon and the adsorption time were the significant factors in the sample preparation procedure.

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