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Optimization of the headspace solid-phase microextraction for determination of glycol ethers by orthogonal array designs

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Abstract

A headspace solid-phase microextraction (HS-SPME), in conjunction with gas chromatography–flame ionization detection for use in the determination of six frequently used glycol ethers at the μg/l level is described. A 75 μm Carboxen–polydimethylsiloxane fiber was used to extract the analytes from an aqueous solution. Experimental HS-SPME parameters such as extraction temperature, extraction time, salt concentration and sample volume, were investigated and optimized by orthogonal array experimental designs. The relative standard deviations for the reproducibility of the optimized HS-SPME method varied from 1.48 to 7.59%. The correlation coefficients of the calibration curves exceeded 0.998 in the μg/l range of concentration with at least two orders of magnitude. The method detection limits for glycol ethers in deionized water were in the range of 0.26 to 3.42 μg/l. The optimized method was also applied to the analysis of glycol ethers in urine and blood samples with the method detection limits ranged from 1.74 to 23.2 μg/l.
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Keywords: Orthogonal array designs; Solid-phase microextraction; Headspace analysis; Glycol ethers

1. Introduction

Glycol ethers have unusual solvent properties, in that they have the solubility characteristics of both ethers and alcohols. These compounds, which are miscible with a large number of organic solvents and water, are used in a wide range of industrial and commercial applications [1]. Glycol ethers are widely used as solvents, detergents, or emulsifiers in products, that include surface coatings, polish removers, liquid cleaning products, etc. For example, ethylene glycol monobutyl ether is a key ingredient in water- or solvent-based coatings and in industrial and consumer cleaning products. The potential toxicity of chemicals is a matter of growing public concern, since many have been reported to have biological activities and have adverse effects on the environment [2,3]. The most prominent and well-recognized targets of glycol ether toxicity are the central nervous, renal, and hematopoeitic systems, as evidenced by the use of laboratory animals as models.

Typically, glycol ethers are separated and detected by gas chromatography (GC) coupled with flame ionization detection (FID), mass spectrometric (MS) detection, or another suitable detection method [4–8]. Analytical methods for the analysis of glycol ethers have been constrained issues that include

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sensitivity, selectivity, and/or extensive sample preparation and much of the work has involved the use of GC–FID. Nevertheless, this technique is limited by its low selectivity for the analytes of interest after their conversion to halogenated derivatives, such as pentafluorobenzyl derivatives [5]. The presence of matrix interference represents an additional limitation to the quantitation of glycol ethers at low levels. In addition, the extraction of polar glycol ethers from aqueous solutions is extremely difficult. In liquid–liquid extraction, solvents used for the extraction are frequently ineffective and may interfere with the analysis of the compounds.

With respect to conventional extraction techniques, solid-phase microextraction (SPME) is an alternative that has been recently developed [9–13]. This procedure is fast, inexpensive, solvent-free, and is an easily automated technique. The headspace (HS) mode of SPME can be extended to the analysis of analytes in complex samples of soils and biological fluids because the fiber coating does not come into contact with the sample directly, thus minimizing matrix interference [14–18]. Thus, HS-SPME in conjunction with GC–FID was employed in the present study to determine glycol ethers without derivatization in various samples. Six frequently used glycol ethers, including ethylene glycol monomethyl ether (EGME), ethylene glycol monoethyl ether (EGEE), ethylene glycol monoisopropyl ether (EGiPE), ethylene glycol monopropyl ether (EGPE), ethylene glycol monobutyl ether (EGBE), and propylene glycol monomethyl ether (PGME) were analyzed.

In order to optimize the HS-SPME conditions, orthogonal array experimental designs were employed. The theory and methodology for orthogonal array experimental design as a chemometric method for the optimization of analytical procedures have been described in detail elsewhere [19–24]. This chemometric method is a sophisticated and cost-effective optimization strategy that can be used to assign experimental factors in a series of experimental trials. The experimental results can then be evaluated by an analysis of variance for determining the main significant factors and two-way interaction factors [24]. A two-level $L_{16}(2^{15})$ orthogonal array and a four-level $L_{16}(4^{5})$ orthogonal array were used to search for the optimum HS-SPME extraction conditions. The influence of the fiber coating on the extraction of glycol ethers was examined first. In addition, the effects of extraction time, extraction temperature, concentration of salts, and sample volume were also evaluated. The optimized conditions were then applied to the analysis of a household detergent and several spiked biological samples.

2. Experimental

2.1. Chemicals

PGME, EGME, EGEE, EGiPE, EGPE and EGBE were all purchased from Fluka (Buchs, Switzerland). HS-SPME was performed with Carbowax–divinylbenzene (CW–DVB), polydimethylsiloxane (PDMS)–DVB or Carboxen–PDMS fibers housed in a manual holder (Supelco, Bellefonte, PA, USA). All SPME fibers were conditioned in a GC injection port by nitrogen carrier gas as recommended by the manufacturer. Water was purified with a Milli-Q water system (Millipore, Bedford, MA, USA) and filtered through a 0.22-μm filter.

2.2. Apparatus

A Hewlett-Packard 5890 Series II gas chromatograph equipped with a split/splitless injection port and a flame ionization detector (Hewlett-Packard, Avondale, PA, USA) was used for the analysis. The column was a 30 m×0.25 mm I.D. DB-Wax fused-silica capillary column with 0.25 μm film thickness (J&W Scientific, Folsom, CA, USA). Nitrogen was used as the carrier gas at a flow-rate of 1.5 ml/min. The detector flow-rates were set at 400 ml/min for air, 30 ml/min for hydrogen, and 30 ml/min for nitrogen (make-up gas). The injector and detector temperatures were maintained at 280 and 250 °C, respectively. The column was kept at 40 °C for 7 min, ramped at 5 °C/min to 75 °C, again ramped at 40 °C/min to 220 °C and then held at 220 °C for 10 min. SPME injections were carried out in the splitless mode and the desorption time was 7 min.

2.3. HS-SPME extraction procedure

A 2-ml volume of sample was placed in a 4-ml

vial along with a magnetic stirring bar (0.8 cm×0.2 cm) and sealed with a PTFE-faced silicone septum. Before inserting the fiber into the headspace above the sample, the vial was preincubated for 5 min in a water bath at the required temperature. A hot plate/stirrer (Corning, NY, USA) was used for maintaining a constant temperature. During the entire extraction procedure, the system was stirred at a constant rate and the fiber was never in contact with the samples. When the extraction was completed, the fiber was immediately introduced into the GC injector port for desorption.

Stock solutions of each analyte were prepared in water. Working solutions were then prepared from these stock solutions by dilution with water. The concentrations of analytes were 5000 μg/l for the optimization study. Heparinized blood samples were obtained from local the Red Cross branch and urine samples were obtained from a male student. Spiked blood and urine samples were prepared by mixing an appropriate volume of stock solutions of glycol ethers to the required concentrations. The spiked samples were analyzed by the optimized HS-SPME extraction procedure.

2.4. Optimization strategy

In the first stage, experimental factors that have significant effects on extraction efficiencies were evaluated by a two-level $L_{16}(2^{15})$ orthogonal array. A statistical analysis (analysis of variance, ANOVA) of the extraction results in the first stage shed some light on the experimental factors that deserved of further attention. In the next stage, the optimum levels of three significant experimental factors were searched according to a four-level $L_{16}(4^5)$ orthogonal array. Table 1 illustrates the assignments of the experimental factors (A, B, and C) and levels (1, 2,

Table 1
Assignment of factors and levels of the optimization experiments using an $L_{16}(4^5)$ orthogonal array design along with the GC–FID responses

Trial No.	Factor					Response						
	A[a]	B[b]	C[c]	–[d]	–[d]	PGME	EGME	EGEE	EGiPE	EGPE	EGBE	SUM
1	1	1	1	1	1	173 482	37 264	110 352	274 680	336 753	589 907	1 522 438
2	1	2	2	2	2	64 800	17 606	41 203	89 279	109 678	162 249	484 815
3	1	3	3	3	3	24 636	7793	15 145	30 943	36 348	51 311	166 176
4	1	4	4	4	4	3274	769	1382	2222	3598	5172	16 417
5	2	1	2	3	4	226 037	54 482	157 929	361 058	527 085	1 004 296	2 330 887
6	2	2	1	4	3	356 413	57 009	227 150	589 777	833 241	1 813 558	3 877 148
7	2	3	4	1	2	35 410	8028	21 807	43 573	62 783	99 821	271 422
8	2	4	3	2	1	18 300	4005	9956	21 287	30 165	47 791	131 504
9	3	1	3	4	2	303 506	54 694	241 176	590 083	913 490	1 968 648	4 071 597
10	3	2	4	3	1	102 013	18 410	79 765	199 722	329 153	857 184	1 586 247
11	3	3	1	2	4	324 728	59 347	254 917	677 003	1 028 304	2 427 993	4 772 292
12	3	4	2	1	3	72 822	12 964	45 360	118 283	165 769	319 918	735 116
13	4	1	4	2	3	165 945	21 572	164 894	531 475	936 859	2 465 590	4 286 335
14	4	2	3	1	4	307 491	40 390	248 937	678 653	1 110 259	2 716 223	5 101 953
15	4	3	2	4	1	313 986	45 392	249 128	685 842	1 092 725	2 711 033	5 098 016
16	4	4	1	3	2	208 871	33 550	164 105	436 091	664 430	1 553 979	3 061 026
E1[e]	547 462	3 052 814	3 308 226									
E2[e]	1 652 740	2 762 541	2 162 209									
E3[e]	2 791 313	2 576 977	2 367 808									
E4[e]	4 386 833	986 016	1 540 105									

[a] Factor A, extraction temperature; level 1, 20 °C; level 2, 40 °C; level 3, 60 °C; level 4, 80 °C.
[b] Factor B, extraction time; level 1, 60 min; level 2, 40 min; level 3, 20 min; level 4, 5 min.
[c] Factor C; salt concentration; level 1, 5 *M*; level 2, 3 *M*; level 3, 1.5 *M*; level 4, 0 *M*.
[d] Dummy factors.
[e] Mean effect of three factors at level 1, 2, 3, or 4.

3, and 4) for the 16 experimental trials. When the optimized extraction conditions were achieved, the extraction was repeated seven times to verify the reproducibility.

3. Results and discussion

For the HS-SPME sampling procedures, several parameters must be controlled to achieve optimum performance, including fiber selection, sample and headspace volume, extraction temperature and time, and the rate of sample agitation. Sample agitation was maintained by stirring at a constant, rapid speed using a magnetic stirrer. The other parameters that affect the efficiency of the HS-SPME method are discussed below.

3.1. Selection of HS-SPME fiber

Three porous polymer fibers, each of which differed in the sorbent-phase were evaluated for the headspace extraction of glycol ethers from an aqueous solution. The adsorption-type fibers used in this study included CW–DVB, PDMS–DVB, and Carboxen–PDMS. Fiber selection was performed for the headspace extraction of a 2-ml aqueous solution containing six glycol ethers. No carryover on the second desorption was found for any of the fibers examined, indicating the complete removal of analytes from the fibers during the initial desorption. The glycol ethers examined were completely separated within 17 min by GC–FID.

The extraction efficiencies of the fibers were based on the average peak area of the analytes for three replicated analyses. The results showed that the amount extracted by the fiber followed a trend. The extraction efficiency of the Carboxen–PDMS fiber was the highest, followed by the PDMS–DVB fiber, and, lastly, the CW–DVB fiber. The use of the CW–DVB fiber has been reported for the extraction of volatile ethers [18], but results obtained here were poor. Only EGPE and EGBE were extracted from an aqueous sample by the CW–DVB fiber. On the basis of the amount extracted onto and then desorbed from the fiber, the Carboxen–PDMS fiber performed best and was selected for the subsequent optimization studies.

3.2. Optimization using a $L_{16}(4^5)$ array

The experimental results of a two-level $L_{16}(2^{15})$ orthogonal array experimental design indicated that the extraction temperature, extraction time, and salt concentration all had significant effects on the extraction efficiency. To optimize the effects of these three factors on the HS-SPME extraction process, a four-level $L_{16}(4^5)$ orthogonal array experimental design was employed. Table 1 illustrates the factor allocations of the orthogonal matrix. In the matrix, the letters A, B, and C represent the extraction temperature, extraction time, and salt concentration, respectively. Numbers 1, 2, 3, and 4 denote four different experimental levels. For each glycol ether, sixteen experimental trials according to the orthogonal array design were conducted. Table 1 provides data on the GC–FID responses for six analytes used in each experimental trial, as well as the mean effects (E1, E2, E3, and E4) for each factor at different levels. The maximum response was achieved at an extraction temperature of 80 °C, a 60 min extraction time, and with 5 *M* NaCl added to the aqueous sample.

3.3. Effects of extraction temperature

In this series of experiments, the temperature of the sample was increased from 20 to 80 °C, at 20 °C increments. Fig. 1 shows the mean effects of temperature on the HS-SPME extraction. The results revealed that the amount of analyte adsorbed is significantly increased with increasing extraction temperature. The mean effects of the FID response

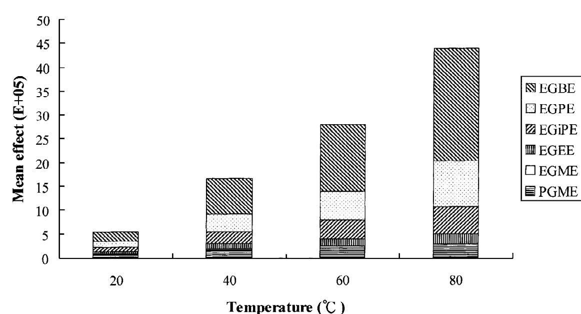

Fig. 1. Effect of extraction temperature on the extraction of glycol ethers from water using the Carboxen–PDMS fiber.

for the six analytes at 80 °C were from three to eleven times higher than that at room temperature. When the extraction temperature was changed from low to high, the amount of analytes evaporated significantly increased. Consequently, an extracting at 80 °C led to the highest efficiency for all analytes. Thus, 80 °C was selected as the temperatures for extracting glycol ethers from the aqueous solutions.

Fig. 1 also reveals the relative extraction amounts for the six glycol ethers. The experimental results indicated that the amount of ethylene glycol ethers extracted by the Carboxen–PDMS fiber increased with the molecular weights of the glycol ethers. Among these ethers, the EGBE was extracted to the greatest extent. However, the relative evaporation rate (*n*-butyl acetate = 1) of these glycol ethers was as follows: PGME (0.7), EGME (0.5), EGEE (0.3), EGPE (0.2) and EGBE (0.07) [1]. These findings indicate that the Carboxen–PDMS fiber had the strongest adsorption effect on EGBE, although the fewest EGBE molecules appeared in the headspace. The extraction of C_2–C_6 hydrocarbons by Carboxen–PDMS showed a similar tendency [25]. These results are probably attributed to the fact that the size and shape of EGBE leads to an optimal fit in the pores in the Carboxen fiber.

3.4. Effects of extraction time

Fig. 2 depicts the mean effects of extraction time on the HS-SPME extraction. The mean effects obtained using a 5-min extraction time were about 40% of that when a 20 min extraction was used. The best responses were obtained for a 60-min adsorption time. However, practical limitations in terms of analysis time must also be taken into account. Since only a slight gain (about 18%) in the mean effect was obtained by extending the extraction time from 20 to 60 min, a 20-min extraction time was chosen as a reasonable compromise for the analysis time for achieving a sufficient extraction onto the fiber.

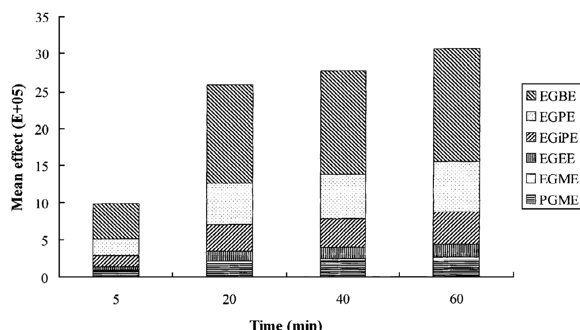

Fig. 2. Effect of extraction time on the extraction of glycol ethers from water using the Carboxen–PDMS fiber.

For HS-SPME extraction, the extraction time of an analyte is dependent on its distribution constants: the headspace/aqueous sample distribution constant (K_{hs}), and the fiber coating/headspace distribution constant (K_{fh}). If the difference in the distribution constant between the fiber coating and the headspace is large, the amounts of material extracted increase and a longer time is required to reach equilibrium. For PGME, the mean effects of a 40 min extraction time were about 96% of that obtained using a 60 min extraction time. Thus, a 60-min extraction could be used as equilibration time for the PGME. The ratios of the amount of material extracted between 40 and 60 min for the other five analytes ranged from 80 to 92%. These results indicate that a 60-min extraction was not sufficient as equilibration time for these five analytes. For a quantitative analysis, it is not necessary for the analytes to approach equilibrium. Only a sufficient loading onto the fiber and a reproducible extraction time are needed. Thus, a 20-min extraction time was selected for subsequent study.

3.5. Effects of ionic strength

By decreasing the solubility of the analyte in water, the amount of analyte partitioned into the headspace and, finally, into the fiber coating increased. For many organic analytes, their solubility in aqueous solution also decreases with increasing ionic strength. Therefore, the effect of sodium chloride on the extraction was investigated over the range of 0.0–5.0 *M* with increasing ionic strength. The results indicated that the mean effect of analyte extracted by the Carboxen–PDMS fiber increased with increasing salt concentration. The mean effect obtained for an aqueous sample that was 5 *M* in NaCl was twice as great as than that for an aqueous sample with no added NaCl. Therefore, all extractions were conducted with 5 *M* NaCl added.

3.6. The optimized HS-SPME conditions

An orthogonal array experimental design has the characteristic of duplicating the operation of experimental factors. Each level of each factor has the effect of repeating four experiments via conducting the experiments using an $L_{16}(4^5)$ orthogonal array. To verify the reproducibility of the optimized HS-SPME conditions, seven extraction trials were performed. The extraction results are shown in Table 2. These finding indicate that the RSDs under optimized extraction conditions were less than 7.59%. A linearity study was also performed using standard aqueous solutions of six analytes at different concentration ranges from 1 to 2500 μg/l. Good linearities were observed for these glycol ethers and the correlation coefficients were found to exceed 0.998.

3.7. Application to detergent and biological samples

The optimized HS-SPME technique was employed in the analysis of a commercial detergent. Fig. 3 illustrates the GC–FID chromatogram of a detergent extracted by HS-SPME. The detergent sample was diluted 10 000 times with ionized water. EGBE was then determined in this detergent sample. The concentration of EGBE in the detergent is 1.14%, which is close to 1% as given by the manufacturer. While the use of EGBE is not forbidden in Taiwan, it is required to specify its content on the product information label.

To further demonstrate that HS-SPME is a useful technique for the screening and quantitation of glycol ethers in biological samples. The optimized HS-SPME sampling parameters for the extraction of glycol ethers were applied to urine and blood samples. Fig. 4 shows the GC–FID chromatograms of glycol ethers from urine samples by HS-SPME. Fig. 4a is a urine sample. Fig. 4b shows a chromatogram of a urine sample spiked with six glycol ethers. Several unidentified peaks are present in the urine sample, but these did not interfere with the identification of glycol ethers.

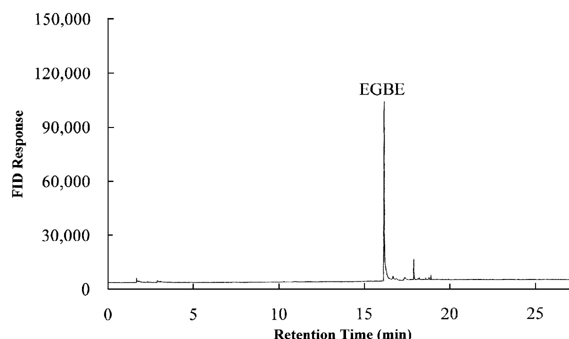

Fig. 3. GC–FID chromatogram of a detergent extracted by the optimized HS-SPME method. Conditions: the Carboxen–PDMS fiber; extraction temperature, 80 °C; extraction time, 20 min; salt concentration, 5 *M* NaCl.

Fig. 5 depicts the GC–FID chromatograms for the glycol ethers in blood samples by HS-SPME. Fig. 5a shows a blood sample and Fig. 5b shows a blood sample spiked with six glycol ethers. All the glycol ethers can easily be identified and no matrix interference was detected. Table 3 presents data on the method detection limits (MDLs) for six glycol ethers at three different matrices. The MDLs correspond to

Table 2
Peak identifications, linear ranges, correlation coefficients, and reproducibilities of the optimized HS-SPME method

Analyte	Peak	Retention time (min)	Linear range (μg/l)	Correlation coefficient (*r*)	Reproducibility[a] (RSD, %)
PGME	1	10.48	5–500	0.9996	4.98
EGME	2	12.01	25–2500	0.9997	6.90
EGEE	3	13.53	5–500	0.9989	1.48
EGiPE	4	13.85	5–500	0.9987	3.36
EGPE	5	15.20	2.5–500	0.9987	4.83
EGBE	6	16.16	1–500	0.9984	7.59

[a] $n=7$.

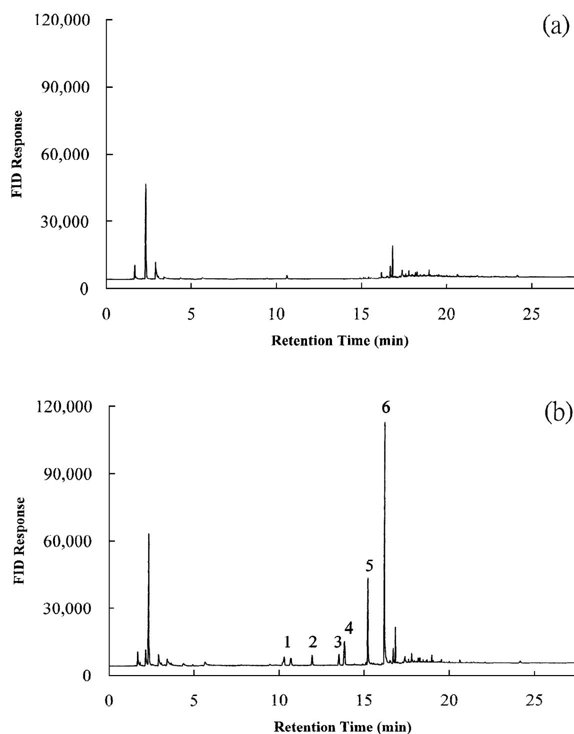

Fig. 4. GC–FID chromatograms of urine samples extracted by the optimized HS-SPME method. (a) Urine sample, (b) urine sample spiked with six glycol ethers. Peaks: 1=PGME, 2=EGME, 3=EGEE, 4=EGiPE, 5=EGPE, 6=EGBE. The concentrations of analytes were 150 μg/l of PGME, EGEE, EGiPE, EGPE, and EGBE and 750 μg/l of EGME. Other conditions as in Fig. 3.

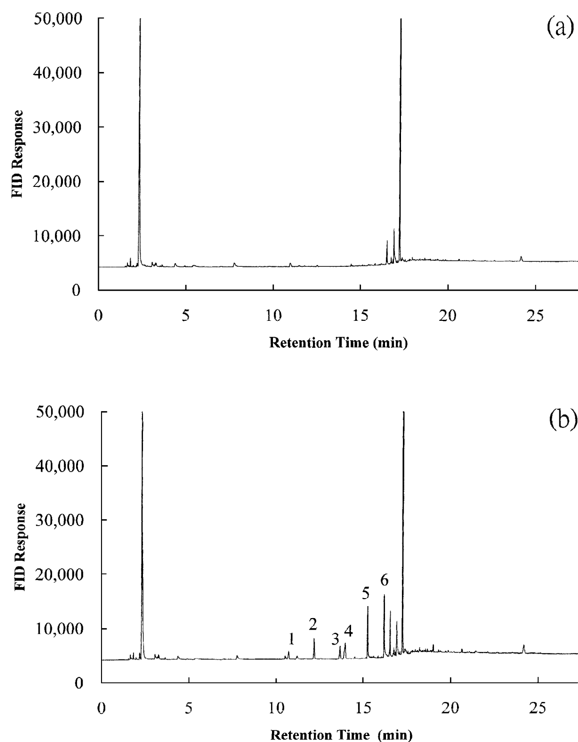

Fig. 5. GC–FID chromatograms of blood samples extracted by the optimized HS-SPME method. (a) Blood sample, (b) blood sample spiked with six glycol ethers. Peaks: 1=PGME, 2=EGME, 3=EGEE, 4=EGiPE, 5=EGPE, 6=EGBE. Conditions as in Fig. 4.

concentrations that gave 3.5 times the standard deviation for eight measurements at a 99% confidence limit. The lowest MDL for each glycol ether, in deionized water, was in the range of from 0.26 to 3.42 μg/l. These results are significantly lower than the detection limits of 10–150 μg/l, reported in a previous SPME study [26]. Even for the urine and blood sample, the MDL was still in the range of 1.74 to 23.2 μg/l. The results are also significantly lower than the liquid–liquid extraction of the analytes in blood samples with a detection limit of 2–3 μg/ml [4]. The above experimental results indicate that the HS-SPME method demonstrates an excellent detection limit without the need for a sample derivatization step. It is not only better than liquid–liquid extraction but is also superior to a direct SPME method.

Table 3
The method detention limits of six glycol ethers in different sample matrices using the optimized HS-SPME method

Analyte	Deionized water[a,b] (μg/l)	Urine[a,c] (μg/l)	Blood[a,d] (μg/l)
PGME	0.95	4.97	8.35
EGME	3.42	6.63	23.2
EGEE	1.12	2.14	9.77
EGiPE	1.02	1.74	7.53
EGPE	0.73	3.36	8.41
EGBE	0.26	2.84	11.3

[a] $n=8$.

[b] Spiked concentrations: PGME, EGEE, EGiPE, EGPE (2.5 μg/l), EGME (12.5 μg/l), and EGBE (1.0 μg/l).

[c] Spiked concentrations: PGME, EGEE, EGiPE, EGPE, EGBE (5.0 μg/l), and EGME (25 μg/l).

[d] Spiked concentrations: PGME, EGEE, EGiPE, EGPE, EGBE (15 μg/l), and EGME (75 μg/l).

4. Conclusions

Experimental results indicate that the optimized HS-SPME method is an efficient method for extracting glycol ethers from aqueous samples. The 75 μm Carboxen–PDMS fiber was found to be the most suitable for extracting the glycol ethers. The optimized HS-SPME conditions for extracting glycol ethers were systematically determined with orthogonal array experimental designs which led to considerable time saving. The relative standard deviations for reproducibility of the optimized HS-SPME method were less than 7.59%. The correlation coefficients of the calibration curves exceeded 0.998 in the μg/l concentration ranges of analytes. Further study demonstrates that this method can be effectively applied in the analysis of glycol ethers in blood and urine samples without the need of derivatization. The MDLs for glycol ethers in various sample matrices were in the sub- to low-μg/l range, significantly lower than previous studies.

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