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Simultaneous Determination of Alkoxyalcohols in Wet Wipes Using Static Headspace Gas Chromatography and Mass Spectrometry

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Alkoxyalcohols are used as solvents or preservatives in various consumer products such as wet wipes. The metabolites of alkoxyalcohols are known to be chronically toxic and carcinogenic to animals. Thus, an analytical method is needed to monitor alkoxyalcohols in wet wipes. The aim of this study was to develop a simultaneous analytical method for 14 alkoxyalcohols using headspace gas chromatography coupled with mass spectrometry to analyze the wet wipes. This method was developed by comparing with various headspace extraction parameters. The linear calibration curves were obtained for the method ($r^2 > 0.995$). The limit of detection of alkoxyalcohols ranged from 2 to 200 ng mL^{-1}. The precision of the determinative method was less than 18.20% coefficient of variation both intra and inter days. The accuracy of the method ranged from 82.86% to 119.83%. (2-Methoxymethylethoxy)propanol, 2-phenoxyethanol, and 1-phenoxy-2-propanol were mainly detected in wet wipes.

Key Words : Alkoxyalcohols, Wet wipes, Static headspace gas chromatography and mass spectrometry

Introduction

Alkoxyalcohols, also called as glycol ethers, are oxygenated hydrocarbons containing either a primary or secondary hydroxyl group, and an ether functional group; therefore, these structural properties allow to mix with both organic and water based formulations.[1,2] These compounds are clear, biodegradable, and less flammable than traditional solvents.[3-5] Because of these chemical properties, alkoxyalcohols are used commercially as solvents in a wide range of personal and household care products including wet wipes.[6]

Wet wipes used for cleansing purposes are moistened piece of paper or non-woven material with water or other liquid, and they provide an excellent environment for the growth of microorganisms such as bacteria, yeast, and molds. Consequently, wet wipes are easily contaminated by microbes.[7,8] To ensure product and consumer safety, the addition of preservatives is necessary.[9] The preservatives in wet wipes as well as in cosmetics that directly contact the skin are mainly alkyl parabens, benzoic acid, and 2-phenoxyalcohols.[10] In particular, 2-phenoxyethanol and 1-phenoxy-2-propanol are similar to and preferred substitutes for parabens in cosmetics and wet wipes.[11,12] However, these compounds are toxic and cause irritation to skin and allergy to animals, particularly for human babies.[13,14] Millions of babies are likely to be exposed to disposable wipes several times on daily basis until they complete toilet training. When these disposable wipes are applied to the skin of the diapered area, which is often exposed to wetness and facial residues, skin irritation or diaper dermatitis may occur.[15] The Postnatal Care Guidelines in the UK do not recommend use of wipes for baby cleansing. Instead, the use of cotton, wool, and water is recommended.[16] Even, the metabolites of other alkoxyethanols such as 2-alkoxyacetaldehydes and alkoxyacetic acids are capable of damaging the chromosomes of human lymphocytes.[17] Cosmetic wipes marketed in the European Union have to be in compliance with the Cosmetics Directive 76/768/EEC and New Cosmetic Products Regulation 1223/2009, which were instituted on 11 July 2013. The limits of 2-phenoxyethanol and 1-phenoxy-2-propanol by the Council of the European Union (EU) and Association of Southeast Asian Nations (ASEAN) in cosmetics are 1% and 2%, respectively.[18,19]

The need of a rapid and reliable method for quantifying and monitoring alkoxyalcohols in wet wipes has become significant. Several studies have reported reversed phase high performance liquid chromatography equipped with UV detector for the detection of 2-phenoxyethanol, parabens benzoates, and benzoic acid esters in cosmetics and in pharmaceutical gels.[20-22] Moreover, gas chromatography and mass spectrometry (GC-MS) method has been described as the determination of 2-phenoxyethanol in ballpoint inks.[23] Recently, the method using micellar electrokinetic chromatography has been reported.[24] Alkoxyalcohols that have relatively lower boiling points and higher vapor pressures

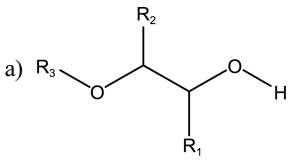
Abbreviation: 2-methoxyethanol (2MeEtOH), 2-ethoxyethanol (EtEtOH), 2-propoxyethanol (2PrEtOH), 2-phenoxyethanol (2PhEtOH), 2-(2-butoxyethoxy)ethanol (2(2BuEt)EtOH), 1-methoxy-2-propanol (Me2PrOH), 1-ethoxy-2-propanol (Et2PrOH), 1-propoxy-2-propanol (Pr2PrOH), 1-butoxy-2-propanol (Bu2PrOH), 1-phenoxy-2-propanol (Ph2PrOH), 1-(2-butoxy-1-methylethoxy)-2-propanol (1(2BuMEEt)2PrOH), (2-methoxymethylethoxy)propanol ((2MeMEEt)PrOH), 3-ethoxy-1-propanol (3EtPrOH), 3-methyl-3-methoxybutanol (3ME3MeBuOH)

than 2-phenoxyethanol were analyzed by GC-MS.[25,26] However, the analytical samples must be diluted frequently using various organic solvents such as ethanol because of the matrix effect. The aim of this study was to optimize simultaneous determination of 14 alkoxyalcohols including 2-phenoxyethanol in wet wipes using headspace gas chromatography mass spectrometry (HS-GC-MS). Preceding studies using HS-GC-MS have reported the determination of volatile compounds in various samples such as water, whole blood, as well as wet wipes.[27-29] In this study, we describe, a method utilizing a HS-GC-MS instrument used for the measurement of volatile compounds. The HS-GC-MS method is expected to be an appropriate method of the detection of alkoxyalcohols in wet wipes because of the lower matrix effect compared to preceding studies.

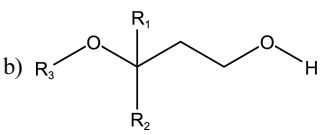
Experimental

Chemicals and Reagents. Reference standards of alkoxyalcohols were purchased from Sigma-Aldrich (St. Louis, MO, USA): 2-methoxyethanol (99.9%), 2-ethoxyethanol (99%), 2-propoxyethanol (99.4%), 2-phenoxyethanol (99%), 2-(2-butoxyethoxy)ethanol (98%), 3-ethoxy-1-propanol (97%), (2-methoxymethylethoxy)propanol (mixture of isomers, 99%), 1-methoxy-2-propanol (99%), 1-ethoxy-2-propanol (97%), 1-propoxy-2-propanol (99%), 1-butoxy-2-propanol (99%), 1-phenoxy-2-propanol (93%), 1-(2-butoxy-1-methylethoxy)-2-propanol (mixture of isomers, 99%), and 3-methyl-3-methoxybutanol (98%). The structure and functional group of 14 alkoxyalcohols are listed in Table 1. 2,3-Dimethyl-1-butanol and 2-phenoxyethanol-d_2 used as internal standards were purchased from Sigma-Aldrich. All standard stock solutions of the 14 alkoxyalcohols were prepared at a concentration of 10% in methanol. A mixture standard solution of six alkoxy-2-propanols was prepared at 2500 μg mL^{-1} in water. This mixture solution was then diluted to 250, 25 and 2.5 μg mL^{-1} with water. The second mixture standard solution of five alkoxyethanols, (2-methoxymethylethoxy)-propanol, 3-ethoxy-1-propanol, and 3-methyl-3-methoxybutanol were mixed at 10000 μg mL^{-1} with water. The second mixture standards solution was diluted to 1000, 100, and 10 μg mL^{-1} with water. 2,3-Dimethyl-1-butanol was dissolved at a concentration of 25 μg mL^{-1} in water, and 2-phenoxyethanol-d_2 was prepared at a concentration of 1000 μg mL^{-1} in methanol. All the standard solutions were stored in septum sealed glass vials (purchased from Supelco, St. Louis, MO, USA) in the dark at 4 °C. Methanol and water were used HPLC grade or higher grade from Burdick and Jackson (Muskegon, MI, USA). Sodium chloride was 99.5% pure (Junsei Chemical Co., Tokyo, Japan).

Table 1. Chemical structure and properties of alkoxyalcohols



R_1	R_2	R_3	Alkoxyalcohols	Abbreviation	Boiling point (°C)	Vapor pressure (hPa at 20-25 °C)
H	H	CH_3	2-Methoxyethanol	2MeEtOH	194	0.10
		CH_2CH_3	2-Ethoxyethanol	2EtEtOH	201	0.07
		$(CH_2)_2CH_3$	2-Propoxyethanol	2PrEtOH	150	1.60
		C_6H_6 (Phenyl group)	2-Phenoxyethanol	2PhEtOH	246	0.01
		$(CH_2)_2O(CH_2)_3CH_3$	2-(2-Butoxyethoxy)ethanol	2(2BuEt)EtOH	231	0.03
CH_3	H	CH_3	1-Methoxy-2-propanol	Me2PrOH	120	15.7
		CH_2CH_3	1-Ethoxy-2-propanol	Et2PrOH	132	9.80
		$(CH_2)_2CH_3$	1-Propoxy-2-propanol	Pr2PrOH	140-160	1.70
		$(CH_2)_3CH_3$	1-Butoxy-2-propanol	Bu2PrOH	171	1.63
		C_6H_6 (Phenyl group)	1-Phenoxy-2-propanol	Ph2PrOH	249	0.03
		$CHCH_3CH_2O(CH_2)_3CH_3$	1-(2-Butoxy-1-methylethoxy)-2-propanol	1(2BuMEEt) 2PrOH	222-232	0.04
		$CH_2CHCH_3OCH_3$	(2-Methoxymethylethoxy)propanol	(2MeMEEt)PrOH	184-197	0.55



R_1	R_2	R_3	Alkoxyalcohols	Abbreviation	Boiling point (°C)	Vapor pressure (hPa at 20 °C)
H	H	CH_2CH_3	3-Ethoxy-1-propanol	3EtPrOH	160-161	0.50
CH_3	CH_3	CH_3	3-Methyl-3-methoxybutanol	3ME3MeBuOH	228-234	0.03

The names of analytes are presented in the form of alkoxyalcohols and abbreviations. a) describes five alkoxyethanols and seven alkoxy-2-propanols, b) describes 3-ethoxy-1-propanol and 3-methyl-3-methoxybutanol.

Table 2. Quantitative and qualifying ions and retention time of alkoxyalcohols and two internal standards

No.	Compounds	Selected ions			$[M]^+$	RT (min)
	Alkoxyalcohols	Q1	Q2	Q3		
ISTD 1[a]	2,3-Dimethyl-1-butanol	59	69	87	102	7.19
ISTD 2[b]	2-Phenoxyethanol-d_2	140	94		140	16.82
1	1-Methoxy-2-propanol	45	47	75	90	7.86
2	1-Ethoxy-2-propanol	59	45	61	104	8.35
3	2-Methoxyethanol	45	58	76	76	8.62
4	2-Ethoxyethanol	59	45	72	90	9.05
5	1-Propoxy-2-propanol	45	73	103	118	9.19
6	2-Propoxyethanol	43	73	104	104	9.82
7	1-Butoxy-2-propanol	45	57	87	132	10.19
8	3-Ethoxy-1-propanol	59	58	86	104	10.56
9	3-Methyl-3-methoxybutanol	73	103		118	11.16
10	(2-Methoxymethylethoxy)propanol	59	73	103	148	11.48/11.55
11	1-(2-Butoxy-1-methylethoxy)-2-propanol	59	103	146	190	13.07/13.15
12	2-(2-Butoxyethoxy)ethanol	57	43	87	162	14.08
13	1-Phenoxy-2-propanol	94	108	152	152	15.94
14	2-Phenoxyethanol	138	94		138	16.86

[a]ISTD 1 is internal standard 1. [b]ISTD 2 is internal standard 2.

Instrument. Samples were analyzed using an Agilent Model 6890A gas chromatograph with a Model 5975C single quadrupole mass spectrometer (GC-MS, Agilent Technologies, Palo Alto, CA, USA) operated in the electron impact ionization (EI) mode. The instrument was also equipped with a static headspace extraction (HSE) autosampler with the ability to control the agitation and temperature (combi-PAL CTC Analytics, AG, Zwingen, Switzerland). The operating conditions used for the HS autosampler are as follows: incubation temperature of 80 °C for the vial, equilibration time of 20 min, agitation speed of 500 rpm, 2 times of strokes, and filling and injection speed of 500 μL/s. The syringe withdrew 1.5 mL sample from HS and was immediately driven into the injection port of the GC. After the injection, helium (99.999%) was used to purge the syringe for 10 min. The GC was equipped with DB-wax capillary column (30 m × 0.25 mm i.d., 0.25 μm film thickness with polyethylene glycol, Agilent Technologies). Helium (99.999 %) was used as carrier gas at a flow rate of 1.0 mL/min. Injection was performed in split mode of 20:1 with an inlet temperature of 250 °C. The oven program used is as follows: 35 °C held for 4 min, ramped to 200 °C at 15 °C/min, and held for 10 min. The transfer line was at 240 °C. Ion source and quadrupole detector were maintained at 150 °C and 230 °C, respectively. A solvent delay was set until 3.5 min, and the detector was shut off after 17.5 min. Alkoxyalcohols in the samples were determined using selected ion monitoring (SIM) mode. The selected ions are listed in Table 2. Chromatographic peaks for target analytes were identified based on the retention time and the presence of qualifying ions. Flat bottom headspace vials (20 mL) and screwed aluminum caps with 20 mm polytetrafluoroethylene (PTFE)-silicon septa were purchased from Interface Co. (Seoul, Korea). Headspace syringes (2.5 mL) were purchased from Agilent Technologies. The HS syringe was maintained at 110 °C to prevent internal condensation and contamination in the control box.

Sample Collection and Preparation. The wet wipes were collected from the market between 2013 and 2014 in Korea. The collected wet wipes were used for multipurpose cleaning including household and industrial applications as well as for the cleansing of skin. A pack of wet wipes was squeezed into 15 mL amber glass vials and stored at 4 C until analysis. For the HSE, an aliquot (5 mL) was then transferred to a 20 mL glass vial contained 2 g of sodium chloride. The two internal standard solutions (20 μL of 25 μg mL^{-1} 2,3-dimethyl-1-butanol and 50 μL of 1000 μg mL^{-1} 2-phenoxyethanol-d_5) were spiked in the aliquots. The vial was sealed with a cap fitted with a Teflon septum. The sealed vial was incubated in the CTC autosampler at 80 °C for 20 min, and then 2.5 mL of extract was immediately injected into the GC-MS for analysis.

Method Validation. The method was validated following IUPAC and MFDS guidelines.[30,31] The instrument was calibrated daily by auto-tuning. Calibration curves were obtained to analyze 5 mL of water samples spiked with standards mixture solutions of alkoxyalcohols. Calibration curves of 14 alkoxyalcohols were used for internal quantification and were drawn at different levels with nominal concentrations ranging from 0.0025 to 40 μg mL^{-1}. Calibration controls across the concentration range were processed to obtain linear regression parameter ($r^2 > 0.995$ for all the compounds). Calibration standards were used to assess the sensitivity and linearity of the method. Accuracy and precision of the method were tested using blank matrices (reagent water) spiked with alkoxyalcohols, and the quality control samples were detected five times per day for five days.

Results and Discussion

Separation of Analytes. One of the most critical areas in determining analytes is the isolation and the highest efficiency of HSE. Moreover, the compounds of interest must be separated from the matrix.[32] Many parameters such as initial holding temperature and time, ramping rate, and carrier gas flow were optimized for the successful analysis of the 14 alkoxyalcohols. Under the described conditions, the retention times of 14 alkoxyalcohols, including the two internal standards, ranged from 7.19 to 16.86 min within 25 min run time as listed in Table 2. A typical gas chromatogram obtained for the analysis of 5 mL water spiked with a standard mixture of the 14 alkoxyalcohols and two internal standards is shown in Figure 1. The peaks of alkoxyalcohols were symmetric and separate from the background components. (2-Methoxymethylethoxy)propanol and 1-(2-butoxy-1-methylethoxy)-2-propanol appeared as two peaks because of the presence of isomers.

Optimization of Static HSE. The HSE depends on the equilibrium between the sample (liquid) phase and gas (HS) phase. If the system contains volatile analytes soluble in the liquid phase, these will distribute between both phases according to the thermodynamically controlled equilibrium.[33,34] The classical means for adjusting sensitivity in HS-GC involve varying temperature, adding salt to the analyte solution (salting out), and using solvent mixtures to fully dissolve the sample and/or enhance vaporization of the analytes.[35] Incubation temperature and time of sample, adding amount of salt, injection volume into GC, and reproducibility were optimized as basic instrumental parameters for simultaneously analyzing 14 alkoxyalcohols. Each HSE parameter was compared to the mean using standard deviation (SD) of the peak responses of five independent samples at same concentration. As shown in Figures 2-5, alkoxy-2-propanols showed higher efficiency of HSE because the vapor pressure of alkoxy-2-propanols is generally higher than other compounds. The vapor pressure of each alkoxyalcohol is listed in Table 1.[36-40]

Effect of Incubation Temperature. The distribution of the analyte between the sample phase and headspace phase upon equilibrium is expressed by a thermodynamically controlled equilibrium constant. By analogy to the common practice in GC, the synonymous partition coefficient (K) is expressed in Eq. (1).

$$[K = C_S/C_G] \quad (1)^{33}$$

where C_S refers to the concentration of the sample and C_G is the concentration of gas phase. Because K is related to vapor pressure, the relationship of K *vs.* temperature (T) can be expressed by Eq. (2).

$$[\log K = B'/T - C'] \quad (2)^{33}$$

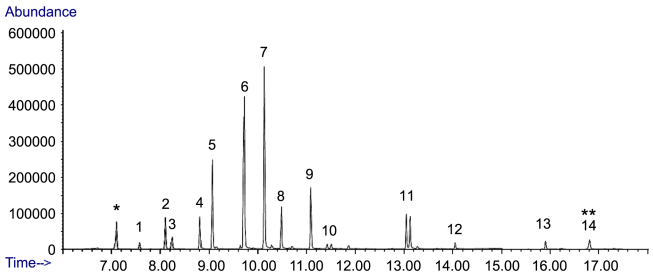


Figure 1. Total ion chromatogram of alkoxyalcohols and two internal standards on a DB-wax column. The names of alkoxyalcohols are listed in Table 2. * is 2,3-dimethyl-1-butanol (ISTD 1) and ** is 2-phenoxyethanol-d_2 (ISTD 2).

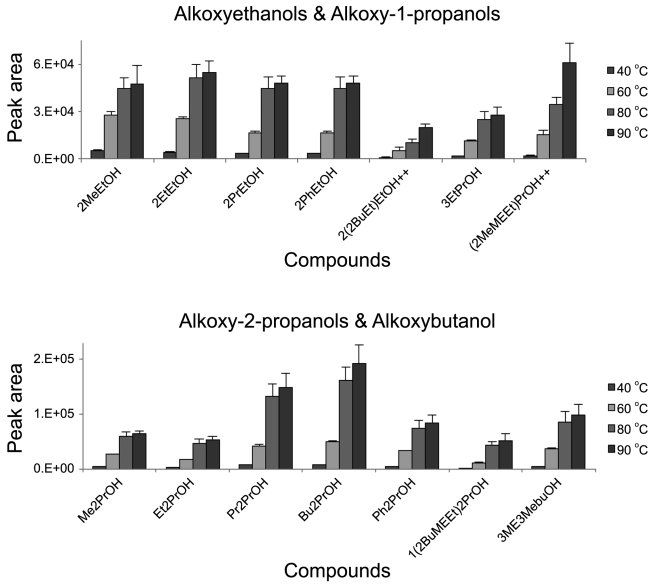


Figure 2. Effect of incubation temperature (40-90 °C) in 5 mL of water spiked with standard mixture of alkoxyalcohols. The names of alkoxyalcohols are listed in Table 2. ++; 2(2BuEt)EtOH and (2MeMEEt)PrOH are depicted in 10 × magnification.

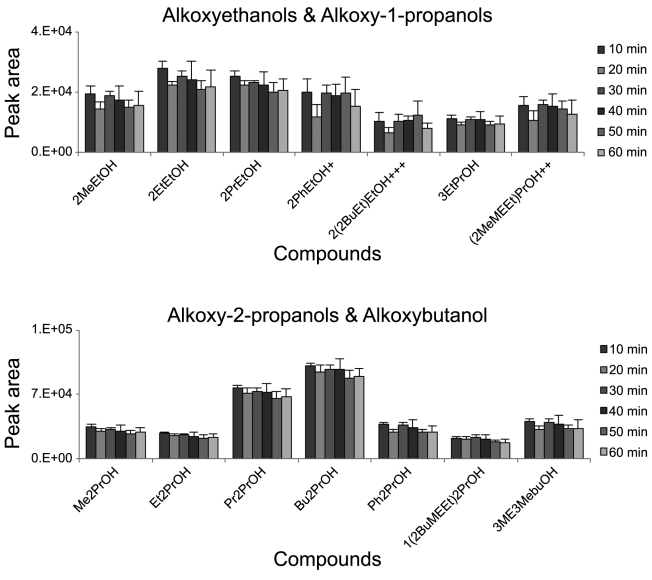


Figure 3. Effect of incubation time (10-60 min) in 5 mL of water spiked with standard mixture of alkoxyalcohols. The names of alkoxyalcohols are listed in Table 2. Following three compounds are depicted to magnify: +; 2PhEtOH-5 times, ++; (2MeMEEt) PrOH-10 times and +++; 2(2BuEt)EtOH-20 times.

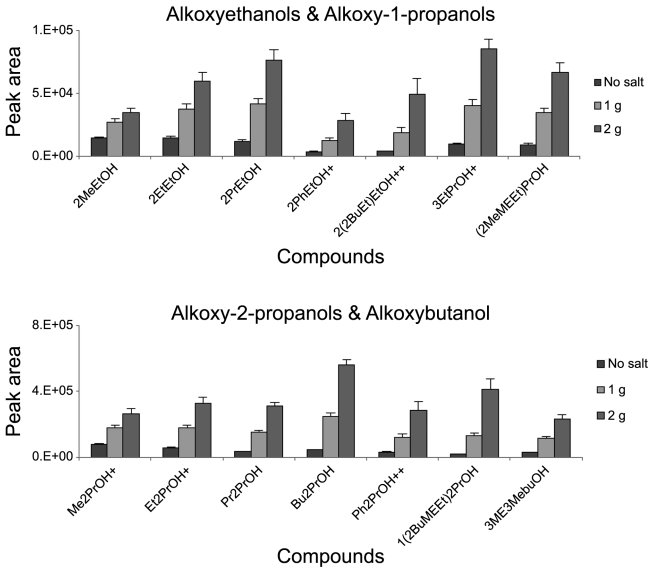


Figure 4. Effect of salt (0-2 g) to 5 mL of water spiked with standard mixture of alkoxyalcohols. The names of alkoxyalcohols are listed in Table 2. Following five compounds are depicted to magnify: +; 2(2BuEt)EtOH, 3EtPrPH, Me2PrOH, Et2PrOH-5 times, ++; Ph2PrOH-10 times.

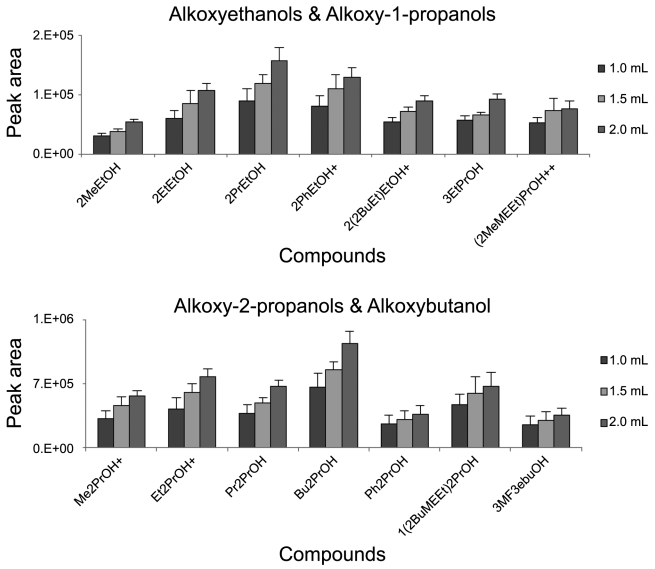


Figure 5. Comparison of injection volume (1-2 mL) onto GC. The names of alkoxyalcohols are listed in Table 2. Following five compounds are depicted to magnify: +; 2PhEtOH, 2(2BuEt)EtOH, Me2PrOH, Et2PrOH-5 times, ++; (2MeMEEt)PrOH-10 times.

where B' and C' are substance-specific constants.[50] Therefore, the concentration of the gas phase (C_G) is proportional to the temperature (T) according to the equations. The efficiency of HSE is increased by increasing incubation temperature. The incubation temperature for alkoxyalcohols ranged from 40 °C to 90 °C. Comparison of incubation temperatures showed peak response at increased temperatures. As shown in Figure 2, higher incubation temperature resulted in higher response of the analyte peaks. However, the extraction at 80 °C was chosen, notwithstanding the best response of peaks at 90 °C because of higher SD of the peak responses (n = 5). The relationship between incubation temperature and efficiency of HS is shown in Figure 2. The SD of the 14 alkoxyalcohols is drawn as an error bar.

Effect of Incubation Time to Reach Equilibrium. For quantitative analysis, constancy and long-term stability in particular are important. Incubation time affects the sensitivity and reproducibility of HSE by equilibrium between the gas phase and sample phase.[34] Thus, the sample in 20 mL of the HS vial was incubated for 10 to 60 min. As shown in Figure 3, the incubation time for alkoxyalcohols showed slight difference. Equilibrium was obtained between the liquid and gas phase at 80 °C within 20 min. According to these results, the incubation at 80 °C for 20 min was chosen for the subsequent experiments.

Effect of Salting Out. The addition of salt to the sample is to enhance vaporization of the analyte.[34] The K of the analytes

Table 3. Calibration curves and detection limits of alkoxyalcohols

Compounds	Calibration			LOD ($\mu g\ mL^{-1}$)	LOQ ($\mu g\ mL^{-1}$)
	Curve	r^2	Range ($\mu g\ mL^{-1}$)		
2-Methoxyethanol	y = 0.0169 x + 0.0019	0.9993	0.08-4	0.08	0.20
2-Ethoxyethanol	y = 0.0339 x – 0.0013	0.9984	0.02-4	0.02	0.04
2-Propoxyethanol	y = 0.2073 x – 0.0092	0.9953	0.05-5	0.05	0.10
2-Phenoxyethanol	y = 1.0033 x – 0.0021	0.9997	0.4-40	0.40	1.00
2-(2-Butoxyethoxy)ethanol	y = 0.1200 x + 0.0323	0.9982	0.4-40	0.40	1.00
1-Methoxy-2-propanol	y = 0.2101 x – 0.0201	0.9972	0.01-10	0.01	0.10
1-Ethoxy-2-propanol	y = 0.3193 x – 0.0164	0.9989	0.0025-10	0.0025	0.40
1-Propoxy-2-propanol	y = 0.8291 x + 0.0140	0.9996	0.005-10	0.005	0.02
1-Butoxy-2-propanol	y = 1.3011 x + 0.0378	0.9993	0.0025-10	0.0025	0.005
1-Phenoxy-2-propanol	y = 0.0956 x + 0.0012	0.9958	0.01-4	0.01	0.02
1-(2-Butoxy-1-methylethoxy)-2-propanol	y = 0.6471 x + 0.0009	0.9963	0.0025-2	0.0025	0.005
(2-Methoxymethylethoxy)propanol	y = 0.2904 x – 0.1648	0.9951	0.2-40	0.20	0.40
3-Ethoxy-1-propanol	y = 0.0218 x – 0.0004	0.9955	0.05-4	0.05	0.10
3-Methyl-3-methoxybutanol	y = 0.0826 x + 0.0016	0.9976	0.008-4	0.008	0.02

between the sample phase and gas phase was affected by the ionic strength.[35] 0, 1 and 2 g of NaCl was added to the sample solution. No more than 2 g of NaCl in 5 mL was used because the solubility of sodium chloride in water is 0.36 g mL^{-1} at 20 °C. As shown in Figure 4, the response of all the alkoxyalcohols is proportional to the amount of salt. The highest response was seen at in the presence of 2 g of NaCl, and this point is approximate to a saturated state. Therefore, the experiment was performed at 80 °C for 20 min by adding 2 g of NaCl to 5 mL of the sample.

Injection Volume. The analysts injected into GC increased with increasing injection volume. Using a 2.5 mL HS syringe, the injection volumes of 1.0, 1.5, and 2.0 mL were tested. Injection of 1.5 mL generally showed about two times larger peak response than that of 1.0 mL injection volume (Figure 5). Although 2.0 mL injection volume showed the best response, 1.5 mL was the most suitable volume considering the SD of the peak responses and the peaks

Table 4. Method validation of alkoxyalcohols

Compounds	Conc. (μg mL^{-1})		Accuracy		Precision	
			Intra	Inter	Intra	Inter
2-Methoxyethanol	Low	0.40	87.13	101.06	16.99	11.02
	Middle	2.00	93.83	104.31	6.29	5.47
	High	4.00	96.24	100.14	9.69	6.22
2-Ethoxyethanol	Low	0.20	109.18	113.62	9.27	13.49
	Middle	0.80	104.70	97.07	12.83	17.96
	High	4.00	90.17	94.95	3.75	8.81
2-Propoxyethanol	Low	0.05	119.34	113.09	6.82	4.81
	Middle	0.50	99.17	96.42	4.94	4.63
	High	5.00	110.89	100.33	8.51	7.23
2-Phenoxyethanol	Low	2.00	98.50	100.97	1.55	3.97
	Middle	8.00	100.55	98.58	1.66	1.87
	High	40.0	99.28	100.27	0.48	2.29
2-(2-Butoxyethoxy)ethanol	Low	2.00	96.91	95.23	7.21	4.53
	Middle	8.00	101.50	98.34	10.94	5.46
	High	20.0	99.95	94.81	3.61	4.89
1-Methoxy-2-propanol	Low	0.05	104.67	102.82	15.66	12.83
	Middle	0.50	109.96	111.32	3.99	13.03
	High	5.00	103.80	95.30	6.68	6.45
1-Ethoxy-2-propanol	Low	0.01	111.31	105.02	16.03	5.10
	Middle	0.50	105.92	104.28	8.52	9.25
	High	10.0	104.80	94.91	2.59	0.86
1-Propoxy-2-propanol	Low	0.01	118.26	108.67	14.88	9.37
	Middle	0.20	102.18	99.42	3.63	4.59
	High	2.00	113.19	102.39	6.11	5.98
1-Butoxy-2-propanol	Low	0.01	118.41	109.27	14.26	12.69
	Middle	0.20	103.42	100.41	7.17	4.54
	High	2.00	109.92	103.65	7.53	6.44
1-Phenoxy-2-propanol	Low	0.04	91.72	107.40	18.20	14.38
	Middle	0.40	92.61	93.57	13.00	17.23
	High	2.0	98.95	106.05	7.07	2.12
1-(2-Butoxy-1-methylethoxy)-2-propanol	Low	0.01	100.64	96.07	7.56	9.20
	Middle	0.10	108.42	101.37	3.49	7.32
	High	1.00	94.61	101.17	7.60	8.11
(2-Methoxymethylethoxy)propanol	Low	0.80	114.36	98.56	13.49	9.43
	Middle	8.00	105.81	106.07	6.79	12.34
	High	20.0	102.72	100.33	3.69	10.59
3-Ethoxy-1-propanol	Low	0.08	94.43	103.58	15.18	9.51
	Middle	0.40	82.86	102.05	14.53	2.90
	High	2.00	95.12	103.71	12.90	4.76
3-Methyl-3-methoxybutanol	Low	0.20	95.04	94.58	15.66	10.34
	Middle	2.00	102.06	102.88	15.50	4.04
	High	4.00	88.54	95.88	13.14	4.89

shape. Therefore, the experiment was performed at 80 °C, for 20 min with 2 g of NaCl, and an injection volume 1.5 mL.

Method Validation. Method validation was developed in terms of the detection and quantification limits, linearity of the calibration curve, repeatability, accuracy, and precision of the 14 alkoxyalcohols. The limit of detection (LOD) of analytes was defined as the lowest detectable concentration over a signal to noise ratio of 3 (S/N ratio > 3) by the instrument under the operating conditions. The limit of quantification (LOQ) was defined as the lowest concentration yielding a S/N of 10.[41] To determine the LOD and LOQ, the water samples were spiked with the mixture standards solutions. The LOD was obtained from 0.0025 μg mL^{-1} to 0.4 μg mL^{-1}. The LOD and LOQ of each analyte are listed in Table 3. Calibration curves were established for mixture standards solutions of each alkoxyalcohol by gradually increasing concentration of each analyte within the concentration range from 0.0025 μg mL^{-1} to 40 μg mL^{-1}. The calibration graph was constructed for peak area ratio against concentration ratio of each alkoxyalcohol to internal standards.[42] An internal standard of 2-phenoxyethanol and 2-(2-butoxyethoxy)ethanol, showing relatively high boiling point and low vapor pressure, was used as 2-phenoxyethanol-d_2. The concentrations of other 12 alkoxyalcohols were calculated using 2,3-dimethyl-1-butanol as the internal standard. The correlation coefficient (r^2) of the calibration curve in this range was > 0.995 (Table 3). The calibration curve equation ($y = ax + b$) was used to calculate the concentration of unknown alkoxyalcohols of analyzed samples in this study. The experiments were performed daily for five days for precision and accuracy of the method. Intra-day validation was detected using a series of five independent samples to evaluate accuracy and precision. The validation samples were spiked at three concentrations (low level = 2 × LOQ, middle, and high level of each alkoxyalcohol within calib-

Table 5. The results of wet wipes for babies (n = 83)

Compound	Average (μg mL^{-1})	Range (μg mL^{-1})	Detection frequency (%)
2-Methoxyethanol	3.58	0.25-6.92	2.22
2-Ethoxyethanol	1.98	1.35-2.61	2.22
2-Propoxyethanol	0.12	0.11-0.12	2.22
2-Phenoxyethanol	2770.83	1.18-7932.01	42.22
2-(2-Butoxyethoxy)ethanol	61.78	2.80-159.65	4.44
1-Methoxy-2-propanol	0.43	0.02-5.74	37.78
1-Ethoxy-2-propanol	0.40	0.02-1.15	3.33
1-Propoxy-2-propanol	N.D.	–	–
1-Butoxy-2-propanol	9.44	0.04-33.59	4.44
1-Phenoxy-2-propanol	0.50	0.04-0.88	5.56
1-(2-Butoxy-1-methylethoxy)-2-propanol	0.47	0.01-0.94	2.22
(2-Methoxymethylethoxy)propanol	0.85	0.85	1.11
3-Ethoxy-1-propanol	2318.62	0.41-4636.82	2.22
3-Methyl-3-methoxybutanol	2191.66	0.32-32861.98	16.67

Table 6. The results of general wet wipes (n = 34)

Compound	Average (μg mL^{-1})	Range (μg mL^{-1})	Detection frequency (%)
2-Methoxyethanol	N.D.	–	–
2-Ethoxyethanol	N.D.	–	–
2-Propoxyethanol	0.10	0.14	2.94
2-Phenoxyethanol	2895.57	1.57-7991.64	70.59
2-(2-Butoxyethoxy)ethanol	51.16	51.16	2.94
1-Methoxy-2-propanol	0.21	0.03-0.68	29.41
1-Ethoxy-2-propanol	1.69	0.02-6.80	17.65
1-Propoxy-2-propanol	0.09	0.09	2.94
1-Butoxy-2-propanol	1.46	0.08-2.84	5.88
1-Phenoxy-2-propanol	3.93	0.05-21.18	17.65
1-(2-Butoxy-1-methylethoxy)-2-propanol	0.17	0.15-0.19	5.88
(2-Methoxymethylethoxy)propanol	1.58	0.76-2.61	11.76
3-Ethoxy-1-propanol	N.D.	–	–
3-Methyl-3-methoxybutanol	0.94	0.74-1.27	8.82

Table 7. The results of wet wipes for cleaning (n = 18)

Compound	Average (μg mL^{-1})	Range (μg mL^{-1})	Detection frequency (%)
2-Methoxyethanol	5.95	5.95	5.56
2-Ethoxyethanol	5.82	5.82	5.56
2-Propoxyethanol	21.36	2.26-31.84	27.78
2-Phenoxyethanol	1660.07	5.65-6004.98	38.89
2-(2-Butoxyethoxy)ethanol	24.01	7.35-57.10	22.22
1-Methoxy-2-propanol	0.13	0.06-0.29	22.22
1-Ethoxy-2-propanol	2.43	2.46	5.56
1-Propoxy-2-propanol	N.D.	–	–
1-Butoxy-2-propanol	98.05	45.01-151.09	11.11
1-Phenoxy-2-propanol	0.88	0.88	5.56
1-(2-Butoxy-1-methylethoxy)-2-propanol	0.44	0.44	5.56
(2-Methoxymethylethoxy)propanol	N.D.	–	–
3-Ethoxy-1-propanol	18.93	1.04-52.65	16.67
3-Methyl-3-methoxybutanol	21588.74	1.10-81985.59	33.33

ration range). The accuracy was calculated, and the recovery was obtained within 100 ± 20%. The minimum level was 82.86% for 3-ethoxy-1-propanol, and the maximum level was 119.34% for 2-propoxyethanol. The precision was calculated as % coefficient of variation (CV) and shown to be < 18.20% (1-phenoxy-2-propanol). The validation of the 14 alkoxyalcohols is listed in Table 4.

Analysis of Wet Wipes. Alkoxyalcohols and their concentrations were determined in wet wipes using the established headspace method. The dilution factor was modified to change applicable concentration range with lower dilution. Most wet wipes contained alkoxyalcohols. The quantitative results from 135 wet wipes are listed in Tables 5-7 including different uses for the wet wipes. 3-Methyl-3-methoxybutanol was found in 16.67% of the baby wet wipes. 2-Phenoxyethanol had the highest detection frequency of 42.22% with the highest concentration of 7932.01 μg mL^{-1} (Table 5). Most of the general wet wipes contained 2-phenoxyethanol (70.59% of 34 samples). The highest concentration of 2-phenoxylethanol in general wet wipes was obtained at 7994.64 μg mL^{-1} (Table 6). Yazar *et al*. reported that the detection frequency of 2-phenoxyethanol in cosmetics and detergents was detected 39% and 19%, respectively.[18] In comparison to our result, the detection frequency of 2-phenoxyethanol seems to follow the similar trend. 2-Phenoxyethanol (< 1%) was used as a preservative in all the samples. This result was in agreement with recommendations of the EU and ASEAN. The wet wipes for cleaning contained 1-butoxy-2-propanol and 3-methyl-3-methoxybutanol as the solvents (Table 7). 1-Butoxy-2-propanol was determined at a higher concentration (maximum level; 151.09 μg mL^{-1}) and detection frequency (11.11%) than wet wipes for directly cleansing skin. Moreover, 3-methyl-3-methoxybutanol had the highest concentration (8.20%). 3-Methyl-3-methoxybutanol manufactured by a Japanese company (Koraray. Co., Japan) is mainly used in cleaners because of its clear, colorless, good biodegradability, and complete water solubility with mild odor characteristics. Because of its high flash point, it is not classified as a flammable chemical under the present EU chemicals regulations.[43]

Conclusion

In this study, a static HSE is found to be a suitable technique for analysis of the 14 alkoxyalcohols in the liquid matrix of wet wipes. The HSE was optimized by controlling the experimental factors such as incubation temperature, time, amount of added salt, and injection volume. This method provides a rapid, reproducible, simple, and effective procedure in quantifying alkoxyalcohols. The use of two internal standards corrects the effect of content in the matrix. The method can be corrected by using both standard addition calibration and experimental correction factors, allowing the quantification of all the compounds studied using GC–MS. The method validation demonstrated good precision, specificity, and accuracy with acceptable recovery and chromatographic resolution.

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