Journal of the Iranian Chemical Society
https://doi.org/10.1007/s13738-019-01690-7

ORIGINAL PAPER

Pivaloyl chloride as a new derivatization agent for parabens and its application in simultaneous derivatization and air-assisted liquid–liquid microextraction of the analytes in hygiene and personal care products

Mir Ali Farajzadeh[1,2] · Mehri Bakhshizadeh Aghdam[1] · Mohammad Reza Afshar Mogaddam[3] · Ali Akbar Alizadeh Nabil[4]

Received: 12 November 2018 / Accepted: 9 May 2019

Abstract

An air-assisted liquid–liquid microextraction method using of an extraction solvent (less dense than water) has been proposed for simultaneous derivatization and extraction of some *p*-hydroxybenzoic acid esters (parabens) in different samples before their determination with gas chromatography-flame ionization detection. The analytes are derivatized by a fast reaction occurring between parabens and pivaloyl chloride (as a derivatization agent) and extracted into toluene (as an extraction solvent) under mild conditions in a test tube. After performing the microextraction procedure, a home-made device (an inverse funnel having a capillary tube) is placed into the tube. A thin film of the extractant accumulated on the surface of the aqueous phase is transferred into the capillary part of the device. A fraction of the organic phase is removed by a microsyringe and injected into the separation system for analysis. Under optimum conditions, detection and quantification limits were between 0.60 and 1.0; and 1.7 and 3.1 ng mL^{-1} in solution; and 6.0×10^{-6} and 1.0×10^{-5}; and 1.7×10^{-5} and 3.1×10^{-5} g kg^{-1} in solid, respectively. The enhancement and enrichment factors were obtained in the ranges of 492–650 and 380–410, respectively. Relative standard deviations were less than 6% ($n=6$) for intra- and less than 9% ($n=4$) for inter-day precisions calculated at a concentration of 50 ng mL^{-1} of each analyte. The calibration graphs were linear with coefficients of determination ≥ 0.994. Finally, the selected parabens were successfully analyzed in various hygiene and personal care products by the proposed method.

Keywords Gas chromatography · Hygiene · Parabens · Derivatization · Air-assisted liquid–liquid microextraction

Abbreviations

AALLME	Air-assisted liquid–liquid microextraction
ER	Extraction recovery
EnF	Enhancement factor
EtP	Ethyl paraben
GC	Gas chromatography
EF	Enrichment factor
MeP	Methyl paraben
PrP	Propyl paraben

Introduction

4-Hydroxybenzoic acid esters (parabens) are widely employed as preservatives in hygiene, cosmetic, and personal care products due to their broad spectrum of antimicrobial activity, ideal physicochemical properties, low toxicity, worldwide legislative acceptance, biodegradability, and cost [1, 2]. However, some studies have shown that parabens can absorb through the skin [3] and cause endocrine disrupting effect [4–6]. To minimize possible risks to human health, European Union law has restricted the use of parabens in hygiene and personal care products. The

✉ Mir Ali Farajzadeh
mafarajzadeh@yahoo.com; mafarajzadeh@tabrizu.ac.ir

[1] Department of Analytical Chemistry, Faculty of Chemistry, University of Tabriz, Tabriz, Iran

[2] Engineering Faculty, Near East University, 99138 Nicosia, North Cyprus, Mersin 10, Turkey

[3] Food and Drug Safety Research Center, Tabriz University of Medical Science, Tabriz, Iran

[4] Pharmaceutical Analysis Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

Published online: 16 May 2019

maximum authorized concentration (MAC) of individual parabens in hygiene and personal care products is 0.04%, and the MAC of overall parabens is 0.08% [7]. Consequently, the development of an analytical method to analyze their levels in personal care products and cosmetic is needful. Many papers on the evaluation of parabens in different samples by high-performance liquid chromatography [8, 9], gas chromatography (GC) [10–13], ultra performance liquid chromatography [14–18], capillary electrophoresis [19], and micellar electrokinetic chromatography [20] have been published. Due to low molecular mass and volatility of parabens, GC is a good option for their analysis. But, they are too polar to be properly separated by GC, and hence, they usually require derivatization before GC analysis for improvement of chromatographic analysis performance. Silylation [21, 22] and acetylation [23, 24] are two common derivatization methods for GC analysis of parabens. These methods have their own limited shortcoming, for example, silylation reagents are moisture-sensitive and some cares must be taken to maintain inert and water-free environment to prevent their deactivation or reduce unwanted side reactions. Moreover, derivatization procedures using the mentioned reagents involve additional steps which increase the time required for sample preparation [25]. In addition to the derivatization, an appropriate sample preparation method is frequently required to isolate the analytes from the complex matrix, concentrate, and make them compatible with the instrumental analytical techniques. Liquid–liquid extraction (LLE) [26], and solid-phase extraction [27] are common pretreatment procedures. However, some disadvantages such as large organic solvent consumption, high cost, and time-consuming make them unappealing for routine analysis. To eliminate these drawbacks, microextraction techniques have been developed. Liquid phase microextraction (LPME) [28] and solid-phase microextraction (SPME) [29] are examples of the microextraction techniques which have been used for the extraction and preconcentration of parabens. The LPME is a simple, rapid, and inexpensive sample preparation method compared to LLE and SPME procedure [30, 31]. In this procedure unlike LLE, only a few microliters of an organic solvent are used. Also, there is no need to expensive and fragile fibers used in SPME. In 2006, Assadi and coworkers developed a new microextraction method namely dispersive liquid–liquid microextraction [32]. This method is based on the dispersion of an extraction solvent (water-immiscible solvent) with the aid of a disperser solvent (water-miscible solvent) into an aqueous sample. Fine droplets of the extraction solvent with a large contact area with the sample solution are formed in this step which lead to achieve high preconcentration and extraction efficiency. The advantages of this method are the simplicity of operation, rapidity, low cost, relatively high extraction recovery (ER), and high enrichment factor (EF). This method has been used in different samples [33, 34]. Despite its advantages, relatively high consumption of dispersive solvent (usually 1 vs. 5 mL aqueous phase) and increasing the solubility of the analytes in the aqueous phase owing to the presence of the disperser are disadvantages of the method. To resolve these problems, some disperser solvent-less techniques such as vortex-assisted liquid–liquid microextraction [35], salt-assisted liquid–liquid microextraction [36], ultrasound-assisted emulsification microextraction, and air-assisted liquid–liquid microextraction (AALLME) [37–39] have been proposed. The turbid solution in AALLME is formed by repeatedly sucking and injecting of a mixture of an aqueous sample solution and a few microliters of an extraction solvent with a syringe in a test tube without using disperser solvent. In a classical AALLME procedure, a water-immiscible organic solvent with density greater than water is used. However, most of these solvents are the halogenated solvents which are hazardous, and their handling is difficult in laboratory. To solve this problem, these solvents are replaced by lighter than water density organic solvents which are low toxic for human and environment.

The main goal of this study was to develop a lighter than water organic solvent AALLME procedure for simultaneous derivatization and extraction of three parabens in different samples. In this process, the analytes are derivatized using a new derivatization agent (pivaloyl chloride) and the derivatized analytes are extracted into a lighter than water organic solvent which is safer than heavier organic solvents. To collect the extraction solvent, a simple device is fabricated. The device is an inverse funnel which is placed into a convenient glass test tube. The proposed method has high enhancement factors (EnFs) and low detection limits. Also, symmetry of the chromatographic peaks of the derivatized products improves with respect to those of the un-derivatized analytes. The other improvement of the method is the collection of the extractant after performing the method by a new device applicable for the extraction solvents lighter than water.

Experimental

Chemicals and reagents

Three parabens including methyl paraben (MeP), ethyl paraben (EtP), and propyl paraben (PrP) with purities > 98% were supplied from Sigma–Aldrich (St. Louis, MO, USA). The tested extraction solvents including *n*-hexane, *n*-octanol, toluene, and xylene were from Merck (Darmstadt, Germany). 3-Picoline (as a catalyst), analytical reagent grade sodium chloride, and methanol were from Merck. Pivaloyl chloride as a derivatization agent was obtained from Sigma–Aldrich. A standard solution of the analytes

was prepared in methanol at a concentration of 1000 mg L^{-1} (each analyte) and stored in a refrigerator at 4 °C. A standard solution of the analytes (each 500 mg L^{-1}) was prepared in a mixture of 3 mL toluene, 0.1 mL 3-picoline, and 1 mL pivaloyl chloride and injected into the separation system (three times in each day) for quality control. Also, the obtained peak areas were used in the calculation of EFs, EnFs, and ERs. Working standard solutions were prepared daily by appropriate dilutions of the standard solution of the parabens prepared in methanol with deionized water (Ghazi Company, Tabriz, Iran).

Instrumentation

The analytes separation and detection were performed with a Shimadzu 2014 gas chromatograph (Kyoto, Japan) equipped with a flame ionization detector (FID) and a split/splitless injector maintained at 290 °C in a splitless/split mode (sampling time 1 min and a split ratio of 1:10). Helium (99.999%, Gulf Cryo, United Arab Emirates) was used as the carrier gas at a constant linear velocity of 30 cm s^{-1}. The separation was carried out on an RTX-1 (30 m × 0.25 mm i.d., film thickness 0.25 µm) capillary column purchased from Restek Corporation (Bellefonte, USA). The column oven temperature was programmed as follows: initial temperature 100 °C (held 1 min) and increased by the rates of 10 °C min^{-1} until 175 °C, 2 °C min^{-1} until 200 °C, and then 30 °C min^{-1} to 290 °C (held 3 min). The FID temperature was maintained at 290 °C. Injections were performed using a zero dead volume microsyringe (1-µL) obtained from Hamilton, Switzerland. Hydrogen gas was generated with a hydrogen generator (OPGU-1500S, Shimadzu, Japan) for FID at a flow rate of 30 mL min^{-1}. The flow rate of air was 300 mL min^{-1}. Separation in gas chromatography-mass spectrometry (GC-MS) was carried out on an HP-5 MS (30 m × 0.25 mm i.d., film thickness 0.25 µm) capillary column (Hewlett-Packard, Santa Clara, USA). Helium (99.9999%, Gulf Cryo, United Arab Emirates) was employed at 1.0 mL min^{-1} as the carrier gas. Temperature programming of the column oven and injector temperature used in the GC-FID experiments was utilized in GC-MS separation. Library searching was performed using the commercial NIST library. Hettich centrifuge model D-7200 (Kirchlengern, Germany) was used in AALLME to expedite phase separation.

Samples

Hygiene and personal care products including toothpaste, sunscreen, hair musk, and face wash gel were purchased from local vendors (Tabriz, Iran). Piroxicam topical gel was bought from local pharmacies. In order to extract the analytes from the samples, 1 g of each sample was mixed with 10 mL methanol and sonicated for 10 min. After centrifugation at 5000 rpm for 10 min, 1 mL of the supernatant was diluted at a ratio of 1:4 with deionized water and subjected to the proposed method.

Procedure for derivatization and microextraction of parabens

5.0 mL of an aqueous standard solution (1 mg L^{-1} of each analyte) or sample (see "Samples" section) along with 7.5%, *w/v*, NaCl were placed into a 10-mL glass test tube. Then 40 µL catalyst (3-picoline), 20 µL derivatization agent (pivaloyl chloride), and 17 µL extraction solvent (toluene) were transferred into the solution. The mixture was repeatedly aspirated into a glass syringe (10-mL) and then expelled into the tube via the syringe needle (five times). A cloudy solution resulted from the dispersion of the fine droplets of toluene into the aqueous solution was formed. In this step, the analytes were rapidly derivatized by pivaloyl chloride and the resultant derivatives were extracted into the toluene droplets. The mixture was centrifuged for 5 min at 5000 rpm. A thin film of the organic phase was floated on the surface of the aqueous phase. The collection device was placed into the tube, and the extractant sat at its narrow section (10 ± 0.5 µL). An aliquot (1 µL) of the collected organic phase was removed using a 1-µL GC microsyringe and injected into the separation system for analysis. The device and the developed derivatization/microextraction procedure are shown in Scheme 1.

EF, ER, and EnF calculation

EF is calculated by the following equation:

$$\mathrm{EF} = \frac{C_{\mathrm{col}}}{C_0} \tag{1}$$

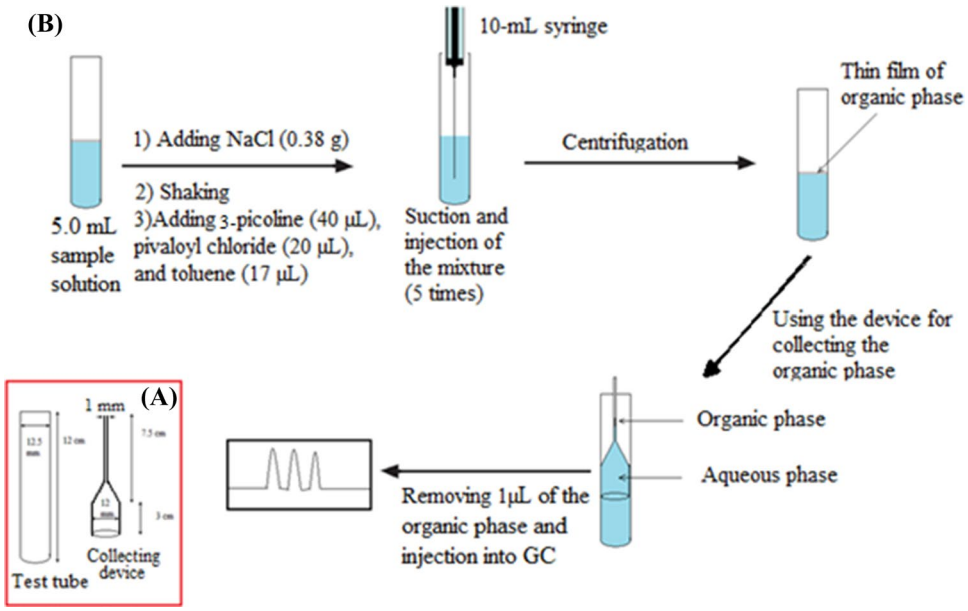
where C_{col} and C_0 are the analyte concentration in the collected organic phase and the initial concentration of the analyte in the sample, respectively. C_{col} is obtained by comparing the results obtained in two following cases: by direct injection of the standard solution of the analytes prepared in a mixture of toluene, 3-picoline, and pivaloyl chloride (see "Chemicals and reagents" section) and injecting the extractant after doing the method.

The following equation was used in ER calculation:

$$\mathrm{ER} = \left(\frac{n_{\mathrm{col}}}{n_0}\right) \times 100 = \frac{C_{\mathrm{col}} \times V_{\mathrm{col}}}{C_0 \times V_{\mathrm{aq}}} \times 100 = \frac{V_{\mathrm{col}}}{V_{\mathrm{aq}}} \times \mathrm{EF} \times 100 \tag{2}$$

where n_0 is total analyte amount, and n_{col} is the extracted amount of analyte. V_{col} and V_{aq} are the volumes of the collected organic phase and aqueous solution, respectively.

EnF is determined by the following equation:



Scheme 1 Extraction device (**a**) and air-assisted liquid–liquid microextraction and derivatization procedure (**b**)

$$\mathrm{EnF} = \frac{\mathrm{slope_{der}}}{\mathrm{slope_{dir}}} \quad (3)$$

$\mathrm{slope_{der}}$ is the calibration curve slope after doing the derivatization/microextraction method, and $\mathrm{slope_{dir}}$ is the calibration curve slope of the direct injection of standard solutions prepared in methanol.

Results and discussion

Selection of extraction solvent

Choosing an appropriate extraction solvent is a key issue in an AALLME method in order to reach an efficient extraction. An extraction solvent in AALLME procedure should meet some requirements such as lower density compared to water (in this study), sparingly soluble in water, high extraction affinity toward the compounds of interest, good gas chromatographic behavior, and forming a cloudy solution during the sucking and injecting cycles. Considering these requirements, four low-density solvents including *n*-octanol ($d = 0.82$ g mL^{-1}), *n*-hexanol ($d = 0.65$ g mL^{-1}), toluene ($d = 0.86$ g mL^{-1}), and xylene ($d = 0.77$ g mL^{-1}) were tested. The initial volumes of the solvents were chosen different to obtain an equal volume for the collected phase (10 ± 0.5 µL). Therefore, 20, 25, 22, and 14 µL of xylene, toluene, *n*-hexanol, and *n*-octanol were used for the extraction of the analytes from the aqueous solution, respectively. According to the obtained results (Fig. 1), toluene is more efficient than other studied solvents owing to chemical structure similarity of toluene and the analytes. So toluene was chosen as the extractant in the next experiments.

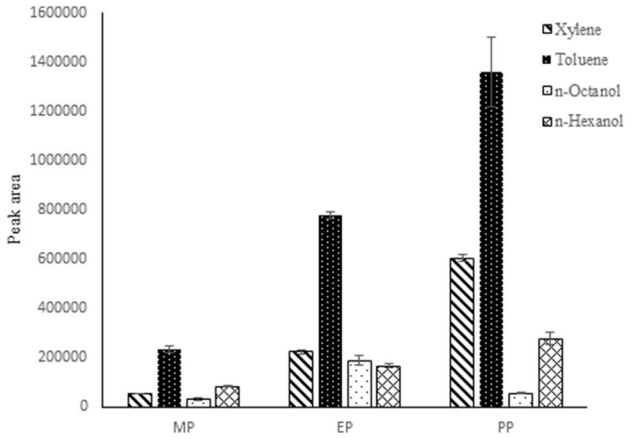


Fig. 1 Selection of extraction solvent. Extraction conditions: Aqueous solution volume, 5 mL; analytes concentrations, 1 mg L^{-1} of each analyte; catalyst type, 3-picoline; catalyst volume, 25 µL; pivaloyl chloride volume, 25 µL; extraction solvent, xylene (20 µL), toluene (25 µL), *n*-octanol (14 µL), and *n*-hexanol (22 µL); extraction cycle numbers, 5 times; centrifugation rate 5000 rpm; and centrifugation time, 5 min. The error bars indicate the minimum and maximum of three determinations

Optimization of extraction solvent volume

The volume of extraction solvent is an important parameter that has impacts on the collected organic phase volume and EF. The extraction solvent volume should be adequate for extraction of the analytes as much as possible but does not dilute them. For this purpose, different volumes of toluene (25–45 µL) were selected. The obtained data showed that (data not shown here) by increasing toluene volume at the mentioned range, the analytical signals decreased continually. It can be attributed to the dilution of the extracted

analytes in the collected phase due to increasing in the collected phase volume from 10 to 32 µL. It is notable that at volumes less than 25 µL, the volume of the collected phase was low and its removal was difficult. So 25 µL toluene was selected as the optimal volume of the extraction solvent for the further steps.

Optimization of derivatization agent volume

In this work, derivatization was performed in an aqueous phase and for the first time pivaloyl chloride was used to convert the parabens to their trimethyl acetyl derivatives. In the derivatization reaction, hydrogen of phenolic group of the parabens replaces with a trimethyl acetyl group. This leads to produce the derivatives which are less polar and more volatile. This improves the chromatographic property of the analytes. The volume of pivaloyl chloride can affect the derivatization yield, the collected phase volume, and the extraction efficiency. To study the effect of derivatization agent volume, different volumes of pivaloyl chloride (15, 20, 25, 30, and 35 µL) were examined. According to the obtained results in Fig. 2, the analytical signals increase by increasing the volume of pivaloyl chloride up to 20 µL and then reduce. It is concluded that at 15 µL, the amount of pivaloyl chloride is not sufficient for complete derivatization. It is noted that in the volumes more than 20 µL pivaloyl chloride, decreasing in the analytical signals can be attributed to dilution effect by increasing the volume of the collected organic phase upon dissolving the excess of the derivatization agent into the organic phase. Finally, 20 µL pivaloyl chloride was chosen for the next experiments.

Optimization of catalyst volume

Parabens are weak acids and addition of an alkaline catalyst such as 3-picoline to the aqueous solution can improve their derivatization yield and rate. 3-Picoline acts as an acid scavenger and accelerates the derivatization reaction. Therefore, optimization of the catalyst volume is necessary for the developed method. For this purpose, different experiments were carried out by adding various volumes of 3-picoline (20–50 µL). Based on the obtained results (Fig. 3), the peak areas of the derivatives increase by increasing the volume of 3-picoline up to 40 µL and then decrease. It should be noted that by increasing 3-picoline volume, the excess of 3-picoline is dissolved into the extraction solvent and the collected phase volume is also increased, and hence, concentrations of the extracted analytes into organic phase are decreased. Subsequently, 40 µL of 3-picoline was used in further experiments.

Study of salt addition

Salting-out effect is observed in most extractive methods. To evaluate the salting-out effect, the developed procedure was performed on the working solutions containing various concentrations of sodium chloride (0, 2.5, 5.0, 7.5, and 10%, *w/v*) using 25, 22, 19, 17, and 13 µL of the extraction solvent, respectively, to reach a constant volume (10 ± 0.5 µL) of the collected phase. The obtained results in Fig. 4 reveal that by increasing sodium chloride concentration up to 7.5%, *w/v*, the analytical signals increase and then decrease gradually. It seems that up to 7.5%, *w/v*, sodium chloride, the salting-out effect leads to an improvement in the migration of the analyte into the organic phase. The reducing in extraction efficiency at a high concentration of sodium chloride (10%, *w/v*) can be attributed to the increased viscosity of the aqueous phase. Considering the results, the next experiments were carried out in the aqueous solutions containing 7.5%, *w/v*, sodium chloride and 17 µL toluene was used as the extraction solvent.

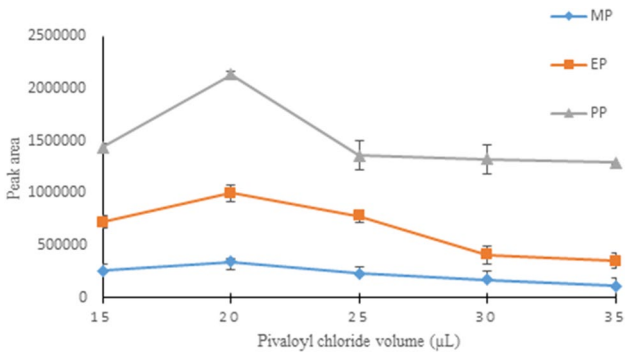


Fig. 2 Study of pivaloyl chloride volume. Extraction conditions are the same as those used in Fig. 1, except 25 µL toluene was used as the extraction solvent

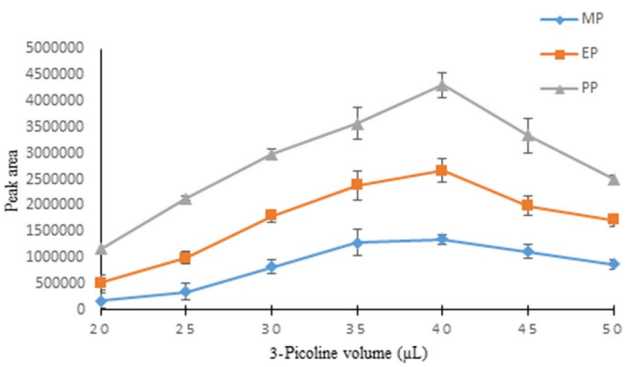


Fig. 3 Study of catalyst volume. Extraction conditions are the same as those used in Fig. 2, except 20 µL pivaloyl chloride was used

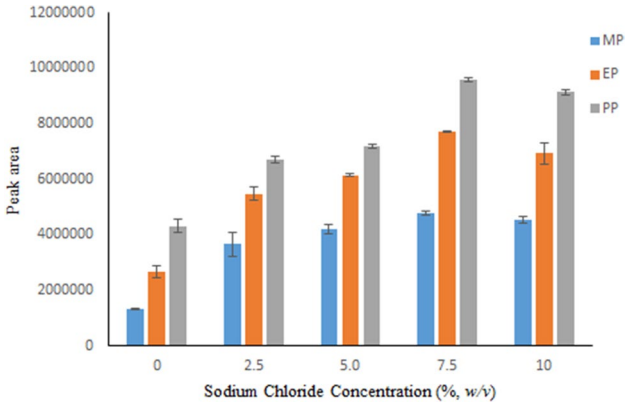


Fig. 4 Effect of salt addition on the performance of the method. Extraction conditions are the same as those used in Fig. 3, except 40 µL 3-picoline was used

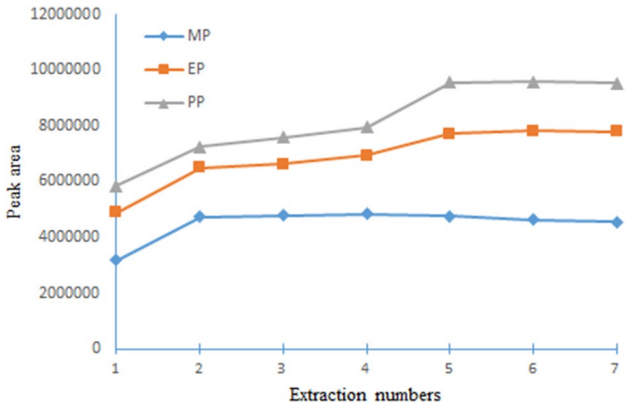


Fig. 5 Study of extraction numbers. Extraction conditions are the same as those used in Fig. 4, except 7.5%, *w/v*, sodium chloride was used

Optimization of extraction cycles number

In this study, the mixture of an aqueous solution, the extraction solvent, and the catalyst was repeatedly sucked into a glass syringe and then expelled into a test tube. Through this action, the analytes convert to the related nonpolar derivatives and extracted into the dispersed extraction solvent. So the number of suction/injection cycles which defined as the "numbers of extraction" can affect the method efficiency and should be optimized. To some extent similar to multiple batch extraction, it is predictable that by increasing extraction numbers, ERs should be increased, too. The effect of extraction numbers was evaluated in the range of 1–7 times. The results in Fig. 5 show that by increasing extraction numbers till the 5th cycle, analytical signals increase and then remain nearly constant. Consequently, 5 times of extraction were selected for the next studies.

Study of centrifugation time and rate

To optimize the centrifugation time and rate, these parameters were examined in the ranges of 1–7 min and 2000–7000 rpm, respectively. The obtained results (data not shown) showed that there is no significant difference in peak areas of the analytes at high centrifuging time and speed. Hence, 5 min and 5000 rpm were chosen in the following experiments, for centrifuging time and speed, respectively.

Analytical features of the proposed method

The method developed in this study was validated in the view of the following features: limit of detection (LOD), limit of quantification (LOQ), EF, ER, EnF, coefficient of determination (r^2), linear range, and repeatability expressed as relative standard deviation (RSD). The results are listed in Table 1. The LODs and LOQs (calculated as S/N = 3 and 10, respectively) were in the ranges of 0.60–1.0 and 1.7–3.1 ng mL^{-1} in solution (6.0×10^{-6} – 1.0×10^{-5} and 1.7×10^{-5} – 3.1×10^{-5} g kg^{-1} in solid), respectively. The r^2 obtained in the range of 0.994–0.996 certified the good linearity of the developed method throughout the studied levels. The precision of the developed method was evaluated by analyzing the standard solutions (50 ng mL^{-1} of each analyte) on the same day and four consecutive days. The RSDs varied from 4–6 and 7–9% for intra- ($n=6$) and inter-day ($n=4$) precisions, respectively. The ERs and EFs were in the ranges of 76–82% and 380–410, respectively. On the other hand, good EnFs ranging from 492 to 650 were obtained due to adding an alkyl group on the analytes by performing the derivatization reaction. This enhanced FID response toward the analytes. It is noted that the obtained LODs (6.0×10^{-6} – 1.0×10^{-5} g kg^{-1}) in this study are completely lower than the MACs (0.04% or 0.4 g kg^{-1}) of the parabens in the studied samples.

Real samples analysis

In order to investigate the performance of the developed method, some hygiene and personal care products including sunscreen, hair musk, toothpaste, face wash gel, and piroxicam topical gel were analyzed under the optimum experimental conditions. All samples were analyzed in triplicate. Typical GC-FID chromatograms of these samples are shown in Fig. 6. According to these chromatograms, there are two suspected peaks eluted in the retention times belong to MeP and PrP in sunscreen and face wash gel samples. To identify these peaks, the samples were also injected into GC-MS after performing the proposed method. The presence of the mentioned analytes in the above samples was verified from GC-MS data. In the case of face wash gel, GC-total ions current-MS chromatogram along with mass data

Table 1 Quantitative features of the derivatization/AALLME-GC-FID method for the selected analytes

Analytes	LOD[a]		LOQ[b]		LR[c]	r^{2}[d]	RSD%[e]		EF ± SD[f]	EnF ± SD[g]	ER ± SD[h]
	In solution (ng mL^{-1})	In solid sample (g kg^{-1})	In solution (ng mL^{-1})	In solid sample (g kg^{-1})			Intra-day	Inter-days			
MP	1.0	1.0×10^{-5}	3.1	3.1×10^{-5}	3.1–12,000	0.994	4	9	380 ± 25	492 ± 25	76 ± 5
EP	0.60	6.0×10^{-6}	1.7	1.7×10^{-5}	1.7–12,000	0.996	6	7	410 ± 20	650 ± 23	82 ± 4
PP	0.70	7.0×10^{-6}	2.2	2.2×10^{-5}	2.2–12,000	0.995	6	8	400 ± 30	610 ± 20	80 ± 6

[a]Limit of detection (S/N = 3)

[b]Limit of quantification (S/N = 10)

[c]Linear range (ng mL^{-1})

[d]Coefficient of determination

[e]Relative standard deviation (n = 6, C = 50 ng mL^{-1} of each analyte) for intra- and (n = 4, C = 50 ng mL^{-1} of each analyte) for inter-day precisions

[f]Enrichment factor ± standard deviation (n = 3)

[g]Enhancement factor ± standard deviation (n = 3)

[h]Extraction recovery ± standard deviation (n = 3)

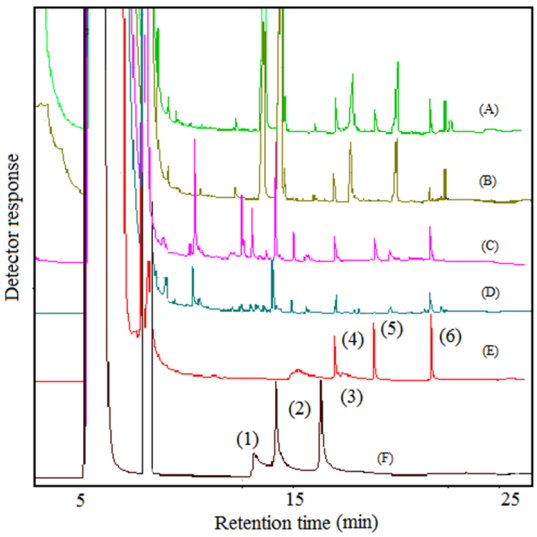


Fig. 6 Typical GC-FID chromatograms of (A) face wash gel spiked with the analytes at a concentration of 250 mg kg^{-1} of each paraben, (B) unspiked face wash gel, (C) sunscreen spiked with the analytes at a concentration of 250 mg kg^{-1} (each analyte), (D) unspiked sunscreen, (E) direct injection of derivatized parabens in toluene (each analyte 250 mg L^{-1}), and (F) standard solution of the analytes in methanol (each analyte 4000 mg L^{-1}). In chromatograms (A) – (D), the method was done and 1 µL of the extractant was analyzed by GC-FID. Peaks identification: (1) MeP, (2) EtP, (3) PrP, (4) derivatized MeP, (5) derivatized EtP, and (6) derivatized PrP

is given in Fig. 7. The concentrations of the analytes in sunscreen and face wash gel calculated based on GC-FID data are summarized in Table 2. Other samples were free of the studied parabens. The matrix effect was investigated using the added-found method. The samples were spiked with the analytes at two concentrations (2.5×10^{-3} and 1.25×10^{-2} g kg^{-1} of each paraben) and subjected to the presented procedure. Mean relative recoveries (compared to recoveries achieved in deionized water spiked at the related concentrations) were obtained in the range of 83–107% (Table 2). The obtained relative recoveries show that samples matrices have a little effect on the performance of the method.

Comparison of the presented method with other methods

Some analytical characteristics including EF, LOD, RSD, and LR of the developed method and other previously published methods for determining parabens in various samples are listed in Table 3. According to the results, the obtained LODs in the presented method are less than those of the other mentioned methods. Repeatability of the developed method is satisfactory, and its RSD % is better than or comparable with the others. In comparison with others, this method has higher EFs. This method uses low volumes of organic reagents and performs microextraction and derivatization in a single step. This method is economical, fast, sensitive, and simple.

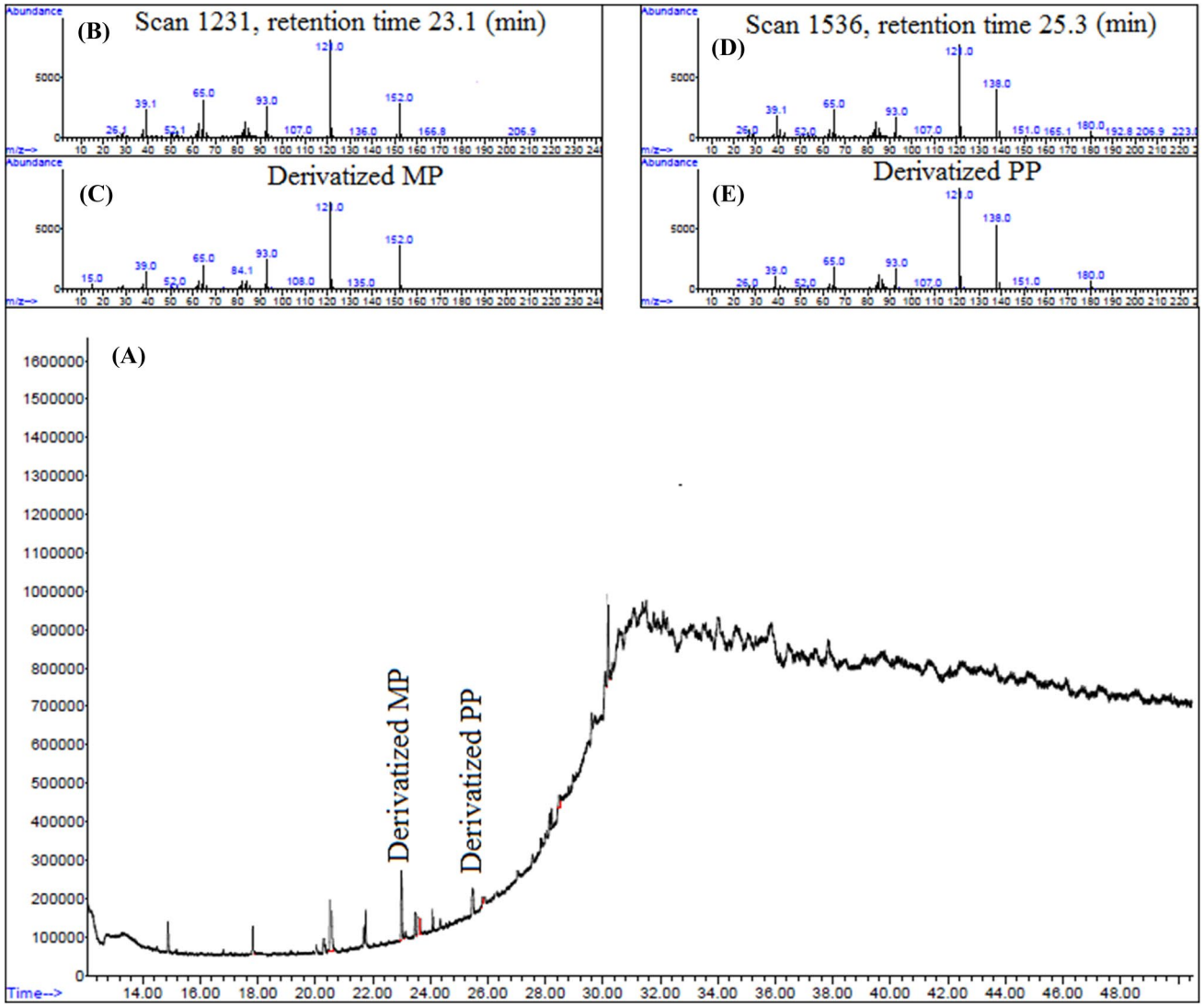


Fig. 7 Typical GC-total ions current-MS chromatogram of face wash gel after performing the proposed method (**a**), and mass spectra of **b** scan 1231 (retention time 23.1 min), **c** derivatized MeP, **d** scan 1536 (retention time 25.3 min), and **e** derivatized PrP

Conclusions

In this work, an easy and fast AALLME method using an extraction solvent lighter than aqueous phase followed by GC-FID analysis was proposed in the determination of parabens in various samples. The derivatization agent was pivaloyl chloride which was used for parabens for the first time. To collect the extractant after performing the method, a new device was utilized. The developed method has some advantages such as ease of operation, high EFs and EnFs, and acceptable repeatability. Moreover, it is economical and less hazardous for the environment due to the low consumption of organic solvents. Derivatization and extraction were performed in a single step. Fast derivatization at room temperature was occurred.

Table 2 Analytes concentration and recovery percent of the selected parabens in real samples

Sample	Added (%, *w/w*)			Found (%, *w/w*) ± standard deviation ($n=3$)			Mean relative recovery (%) ± standard deviation ($n=3$)		
	MP	EP	PP	MP	EP	PP	MP	EP	PP
Sunscreen	–	–	–	$1.6\times10^{-3}\pm2.0\times10^{-5}$	n.d.[a]	$7.5\times10^{-4}\pm1.0\times10^{-5}$	–	–	–
	2.5×10^{-4}	2.5×10^{-4}	2.5×10^{-4}	$1.81\times10^{-3}\pm1.0\times10^{-5}$	$2.45\times10^{-4}\pm1.0\times10^{-5}$	$1.0\times10^{-3}\pm1.0\times10^{-5}$	92 ± 4	98 ± 5	100 ± 5
	1.25×10^{-3}	1.25×10^{-3}	1.25×10^{-3}	$2.9\times10^{-3}\pm8.0\times10^{-5}$	$1.3\times10^{-3}\pm5.0\times10^{-5}$	$1.81\times10^{-3}\pm8.0\times10^{-5}$	104 ± 6	104 ± 4	89 ± 6
Toothpaste	–	–	–	n.d.	n.d.	n.d.	–	–	–
	2.5×10^{-4}	2.5×10^{-4}	2.5×10^{-4}	$2.3\times10^{-4}\pm1.0\times10^{-5}$	$2.07\times10^{-4}\pm1.0\times10^{-5}$	$2.4\times10^{-4}\pm2.0\times10^{-5}$	92 ± 4	83 ± 4	96 ± 8
	1.25×10^{-3}	1.25×10^{-3}	1.25×10^{-3}	$1.34\times10^{-3}\pm7.5\times10^{-5}$	$1.28\times10^{-3}\pm6.0\times10^{-5}$	$1.28\times10^{-3}\pm8.0\times10^{-5}$	107 ± 6	102 ± 5	102 ± 6
Face wash gel	–	–	–	$3.0\times10^{-3}\pm6.0\times10^{-5}$	n.d.	$7.0\times10^{-4}\pm1.0\times10^{-5}$	–	–	–
	2.5×10^{-4}	2.5×10^{-4}	2.5×10^{-4}	$3.24\times10^{-3}\pm1.0\times10^{-5}$	$2.25\times10^{-4}\pm1.0\times10^{-5}$	$9.3\times10^{-4}\pm2.0\times10^{-5}$	96 ± 4	90 ± 4	92 ± 8
	1.25×10^{-3}	1.25×10^{-3}	1.25×10^{-3}	$4.21\times10^{-3}\pm6.0\times10^{-5}$	$1.18\times10^{-3}\pm6.0\times10^{-5}$	$1.85\times10^{-3}\pm6.0\times10^{-5}$	97 ± 5	94 ± 5	92 ± 5
Hair musk	–	–	–	n.d.	n.d.	n.d.	–	–	–
	2.5×10^{-4}	2.5×10^{-4}	2.5×10^{-4}	$2.2\times10^{-4}\pm1.0\times10^{-5}$	$2.4\times10^{-4}\pm1.0\times10^{-5}$	$2.35\times10^{-4}\pm2.0\times10^{-5}$	88 ± 4	96 ± 4	94 ± 8
	1.25×10^{-3}	1.25×10^{-3}	1.25×10^{-3}	$1.29\times10^{-3}\pm5.0\times10^{-5}$	$1.24\times10^{-3}\pm8.0\times10^{-5}$	$1.18\times10^{-3}\pm8.0\times10^{-5}$	103 ± 4	99 ± 6	94 ± 6
Piroxicam topical gel	–	–	–	n.d.	n.d.	n.d.	–	–	–
	2.5×10^{-4}	2.5×10^{-4}	2.5×10^{-4}	$2.3\times10^{-4}\pm1.0\times10^{-5}$	$2.3\times10^{-4}\pm2.0\times10^{-5}$	$2.4\times10^{-4}\pm1.0\times10^{-5}$	92 ± 4	92 ± 8	96 ± 4
	1.25×10^{-3}	1.25×10^{-3}	1.25×10^{-3}	$1.15\times10^{-3}\pm6.0\times10^{-5}$	$1.24\times10^{-3}\pm5.0\times10^{-5}$	$1.21\times10^{-3}\pm8.0\times10^{-5}$	92 ± 5	99 ± 4	97 ± 6

[a]Not detected

Table 3 Comparison of the proposed method with other methods in the extraction and determination of the selected parabens

Method	Sample	LR[a]	RSD%[b]	LOD[c]	EF[d]	References
DLLME-GC-FID[e]	Water	–	5.9–7.4	2.5–22	70–210	[24]
HF-LPME-GC-FID[f]	Facial tonic	–	4.5–8.9	5.1–18	–	[37]
DLLME-GC-FID[e]	Personal care products and food samples	5–30,000	2–3	5.0–15	100–276	[33]
AALLME–GC–FID[g]	Hygiene and personal care products	3.1–12,000	4–6	0.60–1.0	380–410	This work

[a]Linear range (ng mL^{-1})

[b]Relative standard deviation

[c]Limit of detection (ng mL^{-1})

[d]Enrichment factor

[e]Dispersive liquid–liquid microextraction-gas chromatography-flame ionization detection

[f]Hollow fiber-liquid phase microextraction-gas chromatography-flame ionization detection

[g]Air-assisted liquid–liquid microextraction-gas chromatography-flame ionization detection

Acknowledgments The authors wish to thank the Research Council of University of Tabriz for the financial support.

References

1. F. Han, Y.Z. He, C.Z. Yu, Talanta **74**, 1371 (2008)
2. E.J. Routledge, J. Parker, J. Odum, J. Ashby, J.P. Sumpter, Toxicol. Appl. Pharmacol. **153**, 12 (1998)
3. M. Soni, I. Carabin, G. Burdock, Food Chem. Toxicol. **43**, 985 (2005)
4. T. Potouridis, E. Berger, W. Püttmann, Anal. Methods **8**, 3466 (2016)
5. P. Darbre, A. Aljarrah, W. Miller, N. Coldham, M. Sauer, G. Pope, J. Appl. Toxicol. **24**, 5 (2004)
6. P.D. Darbre, P.W. Harvey, J. Appl. Toxicol. **28**, 561 (2008)
7. M. Soni, S. Taylor, N. Greenberg, G. Burdock, Food Chem. Toxicol. **40**, 1335 (2002)
8. C. Almeida, J. Nogueira, J. Chromatogr. A **1348**, 17 (2014)
9. Q. Zhang, M. Lian, L. Liu, H. Cui, Anal. Chim. Acta **537**, 31 (2005)
10. R. Djatmika, C.C. Hsieh, J.M. Chen, W.H. Ding, J. Chromatogr. B **1036**, 93 (2016)
11. R. Aznar, B. Albero, C. Sánchez-Brunete, E. Miguel, I. Martín-Girela, J.L. Tadeo, Environ. Sci. Pollut. Res. **24**, 7911 (2017)
12. P. Canosa, I. Rodriguez, E. Rubi, R. Cela, Anal. Chem. **79**, 1675 (2007)
13. A. Azzouz, A.J. Rascón, E. Ballesteros, J. Pharm. Biomed. Anal. **119**, 16 (2016)
14. L. Schlittenbauer, B. Seiwert, T. Reemtsma, Anal. Bioanal. Chem. **408**, 1573 (2016)
15. M.A. Qadir, M. Ahmed, M.S. Tahir, A. Shakoor, M.I. Shafiq, S. Shahzad, A. Ali, Lat. Am. J. Pharm. **35**, 869 (2016)
16. S.A. Ahmad, M. Ahmed, M.A. Qadir, M.I. Shafiq, Y. Safa, N. Awan, S. Shahzad, A. Ali, M. Feroz, Z.U. Khokhar, Lat. Am. J. Pharm. **35**, 1626 (2016)
17. T. Wu, C. Wang, X. Wang, Q. Ma, Int. J. Cosmet. Sci. **30**, 367 (2008)
18. M. Mincea, I. Lupşa, I. Talpoş, V. Ostafe, Acta Chromatogr. **21**, 591 (2009)
19. U. Alshana, N. Ertaş, N.G. Göğer, Food Chem. **181**, 1 (2015)
20. J.Q. Huang, C.C. Hu, T.C. Chiu, Int. J. Cosmet. Sci. **35**, 346 (2013)
21. R. Djatmika, W.H. Ding, ALCHEMY J. Chem. **5**, 55 (2016)
22. M.K.R. Mudiam, R. Jain, R. Singh, Anal. Methods **6**, 1802 (2014)
23. Z. Hui Ting, E.M. Ding, W.H. Ding, J. Chromatogr. B **1058**, 14 (2017)
24. M. Vila, M. Celeiro, J.P. Lamas, C. Garcia Jares, T. Dagnac, M. Llompart, J. Hazard. Mater. **323**, 45 (2017)
25. A. Prichodko, E. Janenaite, V. Smitiene, V. Vickackaite, Acta Chromatogr. **24**, 589 (2012)
26. E. Ibrahim, R. Lippincott, L. Brenner, I. Suffet, R. Hannah, J. Chromatogr. A **393**, 237 (1987)
27. E. Blanco, M. del Carmen Casais, M. del Carmen Mejuto, R. Cela, Anal. Chim. Acta **647**, 104 (2009)
28. A. Jain, S. Soni, K.K. Verma, J. Liq. Chromatogr. Relat. Technol. **38**, 82 (2015)
29. M. Díaz-Álvarez, S.P. Smith, D.A. Spivak, A. Martín-Esteban, J. Sep. Sci. **39**, 552 (2016)
30. E. Stansiz, J. Werner, A. Zgoła-Grzes´kowiak, Trends. Anal. Chem. **61**, 54 (2014)
31. M.I. Pinto, G. Sontag, R. Bernardino, J. Noronha, Microchem. J. **96**, 225 (2010)
32. M. Rezaee, Y. Assadi, M.R.M. Hosseini, E. Aghaee, F. Ahmadi, S. Berijani, J. Chromatogr. A **1116**, 1 (2006)
33. R. Jain, M.K.R. Mudiam, A. Chauhan, RChR Murthy, H.A. Khan, Food Chem. **141**, 436 (2013)
34. S.M. Sorouraddin, M.R. Afshar Mogaddam, J. Iran Chem. Sci. **13**, 1093 (2016)
35. Z.H. Yang, D.H. Liu, W.T. Zhao, T. Wu, Z.Q. Zhou, P. Wang, J. Sep. Sci. **36**, 916 (2013)
36. M. Gupta, A. Jain, K.K. Verma, Talanta **80**, 526 (2009)
37. M.A. Farajzadeh, M.R. Afshar Mogaddam, Anal. Chim. Acta **728**, 31 (2012)
38. M.A. Farajzadeh, L. Khoshmaram, Food Chem. **141**, 1881 (2013)
39. M.A. Farajzadeh, S.M. Sorouraddin, M.R. Afshar Mogaddam, J. Sep. Sci. **38**, 2470 (2015)