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Detection and Determination of some Migrated Chemicals from Plastic Containers into Different Drinks and Liquids Using Dispersive Liquid-liquid Microextraction Prior to Gas Chromatography

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Migration of chemicals from plastic containers into drinks and liquids is supposed to be a hazardous phenomenon resulting in many health problems. Sample preparation is of great importance due to trace amounts analysis of these compounds. In this research, dispersive liquid-liquid microextraction is applied for the extraction and preconcentration of the migrated compounds prior to their detection and determination by gas chromatography equipped with mass spectrometry or flame ionization detector. The method is based on forming droplets of a water-immiscible organic solvent (extractant) into an aqueous phase using a disperser solvent. As a result, there would be a large contact area between the extractant and aqueous phase containing the analytes which boosts mass transfer. After centrifuging, the extractant is sedimented at the bottom of the aqueous phase and an aliquot of it is removed and injected into the separation system. Various experimental conditions influencing the extraction efficiency were optimized. Under the optimum conditions, the extraction recoveries were ranged from 52-63%. Also, the enrichment factors for the target compounds were calculated to be in the range of 2600-3150. The linear ranges were achieved in the range of 0.61-1000 μg l^{-1}. The relative standard deviations were ≤ 7.2% for intra- (n = 6) and inter-day (n = 4) precisions at a concentration of 20 μg l^{-1} of each analyte. The limits of detection were in the range of 0.18-0.38 μg l^{-1}. Eventually, the applicability of the proposed method for appraising the migrated compounds from plastic containers including butylated hydroxy anisole, butylated hydroxy toluene, bisphenol A, dibutyl phthalate, diethyl phthalate, di-*iso*butyl phthalate, and *p*-xylene was evaluated by analyzing them in different drinks and liquids stored in the plastic bottles.

Abbreviations: ACN, Acetonitrile; BHA, Butylated hydroxy anisole; BHT, Butylated hydroxy toluene; BPA, Bisphenol A; DBP, Dibutyl phthalate; DEP, Diethyl phthalate; DIBP, Di-*iso*butyl phthalate; DLLME, Dispersive liquid-liquid microextraction; EF, Enrichment factor; ER, Extraction recovery; FID, Flame ionization detector; GC, Gas chromatography; IPA, *Iso*-phthalic acid; LOD, Limit of detection; LOQ, Limit of quantification; LR, Linear range; MEG, Mono ethylene glycol; MS, Mass spectrometry; PET, Polyethylene terephthalate; RSD, Relative standard deviation; TPA, Terephthalic acid; 1,2-DBE, 1,2-Dibromoethane; 1,1,2-TCE, 1,1,2-Trichloroethane

Keywords: Plastic bottles, Phthalate esters, Antioxidants, Endocrine disruptors, Dispersive liquid-liquid microextraction, Gas chromatography

INTRODUCTION

The conditions of drinks, especially water, that creatures intake is of great importance. The quality of drinks consumed by a human is much more significant and must be carefully analyzed since some human's diseases are directly linked to the quality of drinks. Obviously, when drinks are enriched with nutrients, people will benefit from, and when

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they are polluted with the contaminants such as chemicals, they can simply cause the most dreadful diseases like cancer, organ damage, infertility, endocrine disruptions, *etc*. [1-3]. The advent of plastic bottles and using them for containing the liquids and drinks in all over the world facilitated many related tasks as like as storage problems, a barrier against foreign pollutants, ease of consumption, cheap production procedure, and transportation of proper drinks to deprived areas. Also, it was supposed that the plastic bottles would thoroughly preserve the safety and purity of water and other drinks, however, investigations disclosed some disadvantages of storing drinks in plastic bottles. So, they cannot be completely inert in contact with aqueous phases. There are different types of drinks stored in plastic bottles such as mineral water, spring water, treated water, carbonated water, physiological serum, water for injection, sterile distilled water, carbonated soft drinks, yogurt drinks, *etc*. Polyethylene terephthalate (PET) is one of the most desirable materials in the production of plastic bottles. The PET bottles were marketed for last four decades and replaced by glass bottles in bazaars [4]. The general purpose is to produce safe and high-quality bottled drinks and liquids but various factors affect the safety of the final product. Some of these factors can be regarded as: leaching the contaminants into mineral waters from surrounding lands such as agricultural and industrial areas, the bottling procedure where the additives and other plastic components can pollute water, and storage conditions in which the plastic components can migrate into drinks depending on the materials have been used in order to produce the bottles which vary among different industries [5,6]. PET is generally synthesized by the prepolymerization of dimethyl terephthalate or terephthalic acid (TPA) with mono ethylene glycol (MEG) followed by a poly condensation using Ge, Sb or Ti catalysts [7,8]. Several chemicals such as monomers, oligomers, additives, catalysts, stabilizers, plasticizers, antioxidants, anti-degradants, lubricants, colorants, and coupling agents are utilized in order to produce favorable bottles [4,9]. *Iso*-phthalic acid, TPA, and MEG are categorized as monomers [10]. Inorganic compounds are used as catalysts or additives in PET production process. Antimony trioxide (Sb_2O_3) is one of the most popular catalysts used in plastic industries [11]. Other metals such as Co, Cr, Fe and Mg have been found in PET bottles too [12]. The amount of metals leached from glass is more than the quantity migrating from PET and this can be the advantage of PET bottled water in comparison to glass-stored water [13].

Plasticizers are of great importance in order to increase the flexibility and softness of bottles [14]. Phthalates and adipates are placed in the category of plasticizers [15]. They may migrate from bottles and enter drink samples because of their low molecular weight and being physically bonded to polymers. Phthalates may also enter water samples from bottling lines, water refinement centers, *etc*. [16,17]. They result in harmful effects like infertility, organ damage, birth defects, cancer, and endocrine disruptions [1]. The US environmental protection agency has authenticated a maximum admissible concentration of 6 μg l^{-1} for di(2-ethyl hexyl) phthalate and 0.4 mg l^{-1} for di(2-ethyl hexyl) adipate in water [18].

Antioxidants are another group that are widely being used in plastic industries. These chemicals are added to polymers in order to prevent or dwindle the oxidation of polymeric compounds [19]. Alkylphenols, butylated hydroxy anisole (BHA), and butylated hydroxy toluene (BHT) are categorized as antioxidants. It is notable that alkylphenols are recognized to be endocrine disrupters [20,21]. It is verified that BHA and BHT are cytotoxic to freshly isolated rat hepatocytes due to the effects of these chemicals on lipid membranes and specifically on mitochondrial membranes [22]. Also, there is a comprehensive research about the effect of both BHA and BHT on rat erythrocytes showing that they might be very detrimental to the circulatory system [23]. Moreover, other studies have declared that high-dosage utilization of phenolic antioxidants engenders carcinogenesis in animals [24]. It is mentioned that the maximum limit of BHA and BHT should not exceed 200 mg kg^{-1} in vegetable oils, either single or in combination [25].

There are some chemical compounds based on benzotriazoles which act as light stabilizers in the PET production industries [26]. Erucamide and oleamide are classified in the group of lubricants. They increase the elasticity and reduce the friction and adhesion of plastics [20]. Bisphenol A (BPA) is another industrial chemical compound which is widely utilized as an additive or monomer in the production process of polycarbonates,

epoxy resins, unsaturated polyester resins, polysulfone resins, polyetherimide resins, flame retardants, *etc*. Tolerable daily intake of BPA is 4 μg kg^{-1} of body weight per day, which is considered to be an endocrine disrupter and several studies have shown its adverse health effects such as cancer, infertility, diabetes, obesity, changes in neural and reproductive systems, cardiovascular and immunological diseases, and damage to genetic materials [27].

Different factors such as storing temperature, physical forces, handling methods, plastic type and presence of oxygen in PET melting procedure can result in thermo-mechanical and thermo-oxidative reactions [28]. Thermal degradation of PET produces many sub-products such as diethylene glycol, aldehydes (formaldehyde, acetaldehyde, and benzaldehyde), aliphatic hydrocarbons, aromatic hydrocarbons (benzene, toluene, and styrene), methanol, *etc*. Presence of aromatic hydrocarbons in drinks like mineral water can origin from both thermal degradation of PET and their existence in the environment due to various industrial uses such as petroleum, gasoline, diesel fuel, and lubricating and heating oil which eventually enters mineral water sources and contaminate them [29]. Despite the great advancements in analytical techniques and devices in last years, sample preparation is still needed to fulfill the trace amounts analysis. Traditional methods like solid phase extraction and liquid-liquid extraction have been utilized for the pretreatment of analytes in real samples. They are helpful but suffer from drawbacks such as the consumption of organic solvents in large volume, and being laborious and time-consuming [30,31]. Up to now, several analytical approaches have been used for the extraction and analysis of the migrated compounds from plastic bottles [32-35]. For example, Choong and co-workers [36] developed a rapid liquid-liquid extraction procedure followed by gas chromatography-flame ionization detection (GC-FID) for the determination of some antioxidants in edible oils and fats. Marce and co-workers [37] developed a solid phase microextraction method with an 85 μm polyacrylate fiber coupled to gas chromatography-mass spectrometry (GC-MS) for determination of some phthalate esters. Yamini and co-workers [38] also developed a headspace solid phase microextraction method by using a graphene/ polyvinylchloride nanocomposite coated fiber for determination of phthalate esters in drinking water and edible vegetable oil samples.

In 2006 an efficient pretreatment method named dispersive liquid-liquid microextraction (DLLME) was introduced [39]. The method is based on forming fine droplets of a water-immiscible organic solvent (extractant) into an aqueous phase using a disperser solvent in order to extract the analytes. As a result, there would be a large contact area between the extractant and aqueous phase containing the analytes which boosts mass transfer. After centrifuging, the extractant is sedimented at the bottom of the aqueous phase or collected on the aqueous phase based on the density of the extraction solvent used. Eventually, a microliter volume of it is taken and injected into a detection system. This method has copious superiorities including ease of operation, rapidity, high enrichment factor (EF) and ER, and little organic solvent consumption.

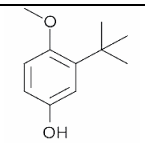
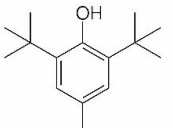
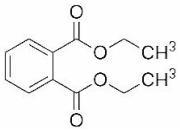
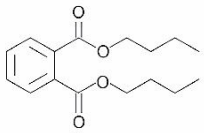
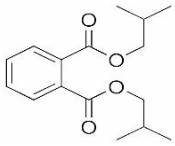
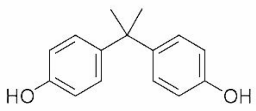
In this study, a comprehensive investigation was fulfilled around the safety of some widely used drinks and liquids stored in plastic containers in Iran. Detection and quantification of the migrated compounds (indicated in Table 1) from plastic containers into different drinks and liquids stored in them, is the purpose of this survey. Moreover, for the first time, a comprehensive investigation of the effects of different storage conditions of the mineral water samples on the migration of the chemicals from plastic containers was performed by employing an effective, reliable, and profitable extraction procedure called DLLME coupled with GC.

EXPERIMENTAL

Chemicals and Solutions

The analytes utilized in the present research containing *p*-xylene (analytical grade), BHA (98.5%) and BHT (99%) were obtained from Merck (Darmstadt, Germany), and diethyl phthalate (DEP) (99.5%), di-*iso*butyl phthalate (DIBP) (99%) and dibutyl phthalate (DBP) (99%) were bought from Sigma-Aldrich (St. Louis, MO, USA). BPA (99.8%) was bought from Dr. Ehrenstorfer (Augsburg, Germany). Acetonitrile (ACN), acetone, methanol, chloroform, sodium chloride, sodium hydroxide and hydrochloric acid (37%, *w/w*) were also supplied from Merck (all were of analytical grade). 2-Propanol (analytical

Table 1. Structure and Physicochemical Properties of the Studied Analytes [40]

Analyte	Structure	Molecular formula	Molecular weight (g mol^{-1})	Boiling point (°C)	Solubility in water at 25 °C (mg l^{-1})	Selected ions (m/z)
BHA		$C_{11}H_{16}O_2$	180.24	268	210	137, 165[a] and 180
BHT		$C_{15}H_{24}O$	220.35	265	1.10	57, 205 and 220
DEP		$C_{12}H_{14}O_4$	222.24	295	1.08	65, 149 and 177
DBP		$C_{16}H_{22}O_4$	278.34	340	11.20	76, 103 and 148
DIBP		$C_{16}H_{22}O_4$	278.35	320	6.20	57, 104 and 148
BPA		$C_{15}H_{16}O_2$	228.29	220	120	91, 119 and 213
p-Xylene		C_8H_{10}	106.16	138	165	77, 91 and 106

[a]The bolded m/z data belong to the base ions in each case.

grade) was purchased from Caledon (Georgetown, Canada). 1,2-Dibromoethane (1,2-DBE), carbon tetrachloride, and 1,1,2-trichloroethane (1,1,2-TCE) (all were of analytical grade) were from Janssen (Beerse, Belgium). Sodium sulfate and sodium nitrate (both were of analytical grade) were supplied from Fluka (Buchs, Switzerland). Deionized water was from Ghazi Co. (Tabriz, Iran) which was utilized to prepare solutions. Methanol was utilized to prepare the stock solution of the analytes with a concentration of 1000 mg l^{-1} of each. Deionized water was also applied in order to prepare working standard solutions by diluting the stock solution.

Samples

Different samples such as three brands of mineral water which were studied chronologically and in different storage

conditions (room temperature, refrigerator, and freezer), two brands of carbonated soft drinks, and one brand of yogurt drink were purchased from local markets (Tabriz, East Azerbaijan Province, Iran). Moreover, two brands of physiological serum and a sterile distilled water were bought from a local drugstore and directly analyzed after purchase. Except the carbonated soft drinks A and B, and the yogurt drink that were diluted with deionized water before performing the method at ratios of 1:2, 1:4 and 1:4, respectively, other samples were used without prior treatment or dilution.

Apparatus

Separation and analysis of the analytes were accomplished by a Shimadzu 2014 gas chromatograph (Kyoto, Japan) equipped with a split/splitless injector operated at 300 °C in a splitless mode and an FID. The linear velocity of 30 cm s^{-1} and a flow rate of 30 ml min^{-1} were fixed for the carrier and make up gasses, respectively using helium (99.999%, Gulf Cryo, United Arab Emirates). An Equity^{TM}-1 capillary column (100% dimethyl siloxane, 30 m × 0.25 mm i.d., and a film thickness of 0.25 µm) (Supelco, Bellefonte, USA) was used to separate the analytes. The initial column oven temperature was fixed at 70 °C for 3 min, then a programmed ramp of 10 °C min^{-1} to 300 °C was applied and retained for 3 min at 300 °C. The temperature of FID was held at 300 °C. Hydrogen gas generated by a hydrogen generator (OPGU-1500S, Shimadzu, Japan) was utilized for FID at a flow rate of 30 ml min^{-1}. The air flow rate for FID was fixed at 300 ml min^{-1}. In order to perform GC-MS analysis, an Agilent 7890A-5975C gas chromatograph-mass spectrometer (Agilent Technologies, CA, USA) containing a split/splitless injector operated in a splitless mode and a quadrupole mass analyzer was applied. The operational conditions of MS were as follows: transfer line temperature, 260 °C; ionic source temperature, 250 °C; mass range, m/z 55-400; electron ionization at 70 eV; acquisition rate, 20 Hz; and detector voltage, -1700 V. A commercial NIST library was used to perform library searching. The separation was done on an HP-5 MS capillary column (30 m × 0.25 mm i.d., and a film thickness of 0.25 µm) (Agilent Technologies, Illinois, USA). Helium was utilized as the carrier gas at a flow rate of 1.0 ml min^{-1}. The temperatures of the injector and the column oven programming were as same as the temperatures utilized in GC-FID previously. A Hettich centrifuge, model D-7200 (Kirchlengern, Germany) was applied for accelerating the separation of the phases after extraction.

Extraction Procedure

An optimized DLLME method was performed in order to extract and preconcentrate the analytes from the aqueous phase. Initially, 50 ml of deionized water containing 1.25 g Na_2SO_4 (2.5%, *w/v*) spiked with the concentration of 0.5 mg l^{-1} (of each analyte) or sample solution (see Sec. 2.2) was transferred into a 70-ml conical glass test tube. Then, 2.5 ml 2-propanol (as a disperser solvent) containing 45 µl 1,2-DBE and 45 µl carbon tetrachloride (as extraction solvents) was quickly injected into the aqueous phase using a 5-ml glass syringe. A cloudy solution containing the fine droplets of the organic phase was appeared which illustrated a successful DLLME process for extraction. Afterward, the resulted solution was centrifuged for 5 min at 3000 rpm, and subsequently, 10 ± 0.5 µl of the extractant containing the extracted analytes was sedimented at the bottom of the test tube. Eventually, 1 µl of the sedimented organic phase was removed and injected into the separation system for a quantitative analysis.

Calculation of EF and ER

The prominent parameters of EF and ER have been illustrated to evaluate the method presented. EF is defined as the ratio of the analyte concentration in the sedimented phase (C_{sed}) to its initial concentration in the aqueous phase (C_0):

$$EF = \frac{C_{sed}}{C_0} \quad (1)$$

ER is defined as the percentage of the total amount of the analyte (n_o) extracted into the sedimented phase (n_{sed}) and the equation bellow was used for its calculation:

$$ER = \frac{n_{sed}}{n_0} \times 100 = \frac{C_{sed} \times V_{sed}}{C_0 \times V_{aq}} \times 100 = EF \times \frac{V_{sed}}{V_{aq}} \times 100 \quad (2)$$

where V_{sed} and V_{aq} stand for the volumes of the sedimented

phase and aqueous phase, respectively.

RESULTS AND DISCUSSION

As stated, this study aims at detecting and quantifying the migrated compounds from plastic containers into different drinks and liquids, due to their detrimental impact on health, by means of DLLME coupled with GC-MS or GC-FID. In order to reach the optimized conditions for the extraction procedure, firstly, BHT, BHA and DEP were selected as the model compounds and the effect of various parameters, such as the type and volume of disperser solvent, the type and volume of extraction solvent, pH, ionic strength, and centrifuging speed and time were investigated. Afterward, under the optimum conditions, various samples were investigated, the migrated compounds from plastic containers were detected by GC-MS, and the corresponding concentrations were determined by GC-FID.

Selection of Extraction Solvent

In microextraction methods, it is critical to choose an appropriate extraction solvent. A proper extraction solvent should contain some features such as suitable extraction capacity of the target compounds with different polarities, low solubility in aqueous phase, acceptable chromatographic behavior (having a good compatibility with the separation system and no interfering peak with the analytes), formation of a cloudy solution in the presence of a disperser solvent, and specially in this case, having high density compared to water to be collected at the bottom of a 70-ml conical test tube after centrifuging. Considering these features, four organic solvents including chloroform, 1,1,2-TCE, 1,2-DBE and carbon tetrachloride were tested to find the suitable solvent. In order to obtain a similar volume (10 ± 0.5 µl) of the sedimented organic phase after the accomplishment of the method, 200 µl of chloroform, 155 µl of 1,1,2-TCE, 120 µl of 1,2-DBE, and 70 µl of carbon tetrachloride were utilized as the extraction solvents. It should be mentioned that in all experiments, 2 ml ACN as the disperser solvent was utilized. Figure 1 illustrates the influence of the type of extraction solvent on the extraction efficiency of the target compounds. As it is obvious, 1,2-DBE results in high ER for BHA, and carbon tetrachloride provides high ERs for BHT and DEP in comparison to other organic solvents. Hence, the mixtures of 1,2-DBE and carbon tetrachloride were opted for the further experiments.

Selection of the Ratio of the Extraction Solvents

Since the plastic containers comprise of various types of chemical compounds with different polarities and solubilities in organic solvents, applying only one extraction solvent may result in deficient microextraction. As a result of this procedure, some compounds cannot be efficiently extracted into the organic phase; as indicated in Fig. 1. In this step, various mixtures of 1,2-DBE and carbon tetrachloride with different ratios were investigated in order to find an optimum ratio for the microextraction procedure. In order to obtain a similar volume of the sedimented organic phase after applying the method (10 ± 0.5 µl), 17:68, 38:57, 52:52, 66:44 and 92:23 (µl:µl) of 1,2-DBE and carbon tetrachloride were utilized for the ratios of 20:80, 40:60, 50:50, 60:40, and 80:20 (%, *v/v*) of the mentioned extraction solvents, respectively. Figure 2 illustrates the effect of using different ratios of the two mentioned extraction solvents on the extraction efficiency of the target compounds. Considering the results, the ratio of 50:50 was selected for the further experiments to have an appropriate ER for BHA beside DEP and BHT.

Selection of Disperser Solvent

A disperser solvent in DLLME method must be miscible with both organic and aqueous phases and be able to disperse the extraction solvent into the aqueous phase. It is prominent that the extraction solvent forms fine droplets into the aqueous phase to obtain a large contact area and finally results in prompt migration of the analytes into the extraction solvent. To investigate this parameter, four solvents such as acetone, ACN, methanol, and 2-propanol were investigated due to their ability to disperse the extraction solvent into the aqueous phase. It is obvious from Fig. 3 that 2-propanol results in high ERs, so it was opted as the disperser solvent to be used in further analysis. It is noted that when 2-propanol was used as a disperser solvent, turbidity of the obtained solution was more than the cases in those ACN, acetone, and methanol were employed. This shows that small droplets of the extraction solvent are produced in the case of 2-propanol compared with the other used disperser solvents.

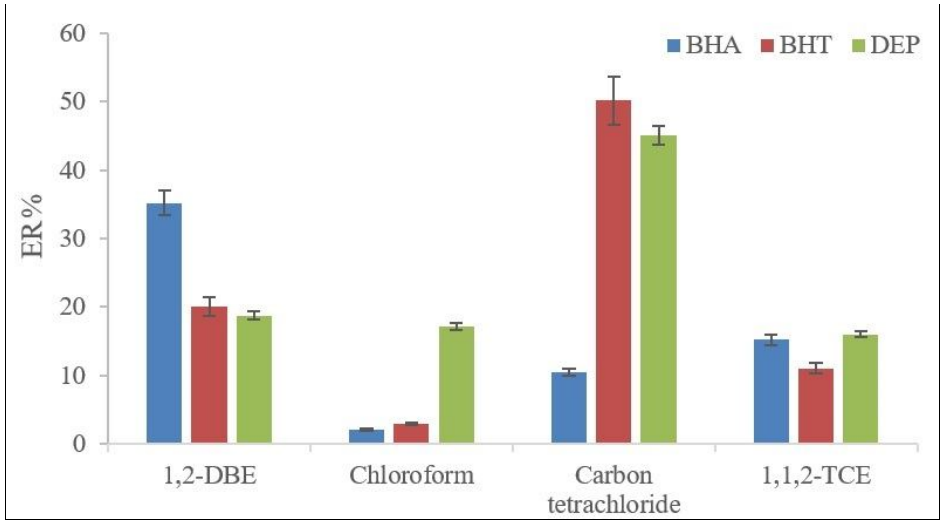


Fig. 1. Effect of extraction solvent type on the ER. Aqueous sample volume, 50 ml deionized water spiked with 0.5 mg l^{-1} of each analyte; disperser solvent (volume), ACN (2.0 ml); extraction solvent, chloroform (200 µl), 1,1,2-TCE (155 µl), 1,2-DBE (120 µl), and carbon tetrachloride (70 µl); centrifugation rate, 5000 rpm; and centrifugation time, 3 min. The error bars show the minimum and maximum of three repeated determinations.

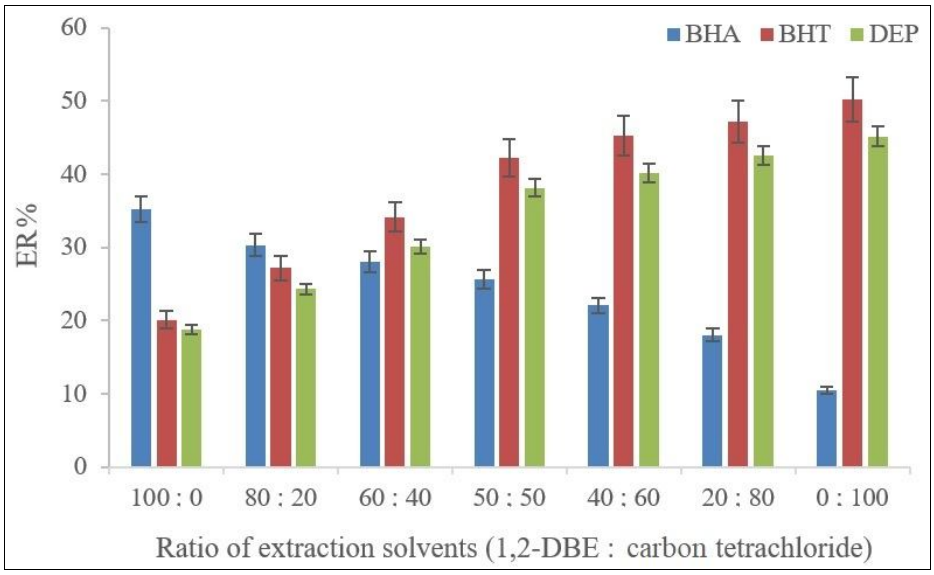


Fig. 2. Effect of the ratio of the extraction solvents on the ER. Extraction conditions are the same as those used in Fig. 1, except different ratios of 1,2-DBE and that carbon tetrachloride were used as the extraction solvent.

Optimization of the Disperser Solvent Volume

The volume of disperser solvent has an inevitable impact on the performance of DLLME procedure. In order to evaluate the effect of this parameter, various volumes of 2-propanol (1.0-3.5 ml) were investigated. The obtained results (Fig. 4) show that the ERs of the target compounds

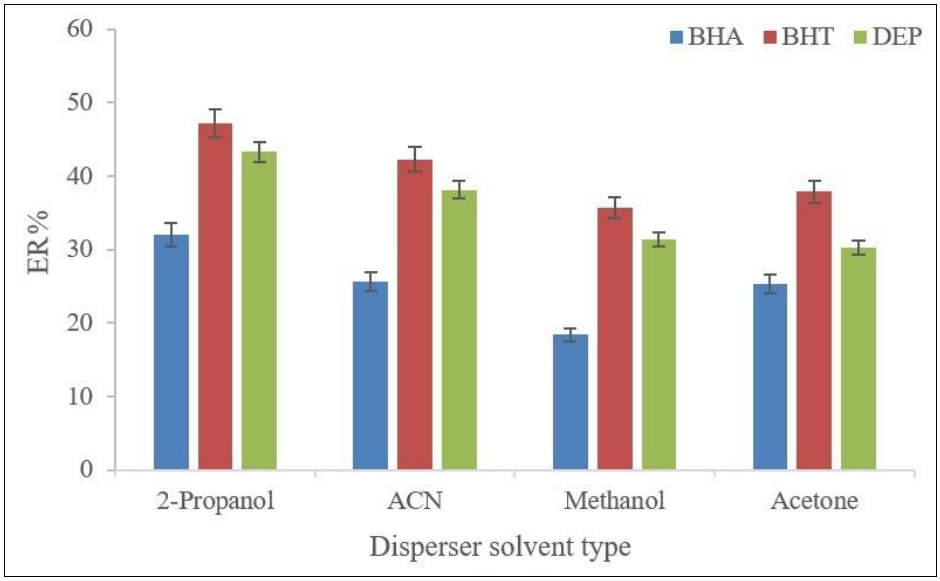


Fig. 3. Effect of disperser solvent type on the ER. Extraction conditions are the same as those used in Fig. 2, except a ratio of 50:50 1,2-DBE and that carbon tetrachloride was used as the extraction solvent.

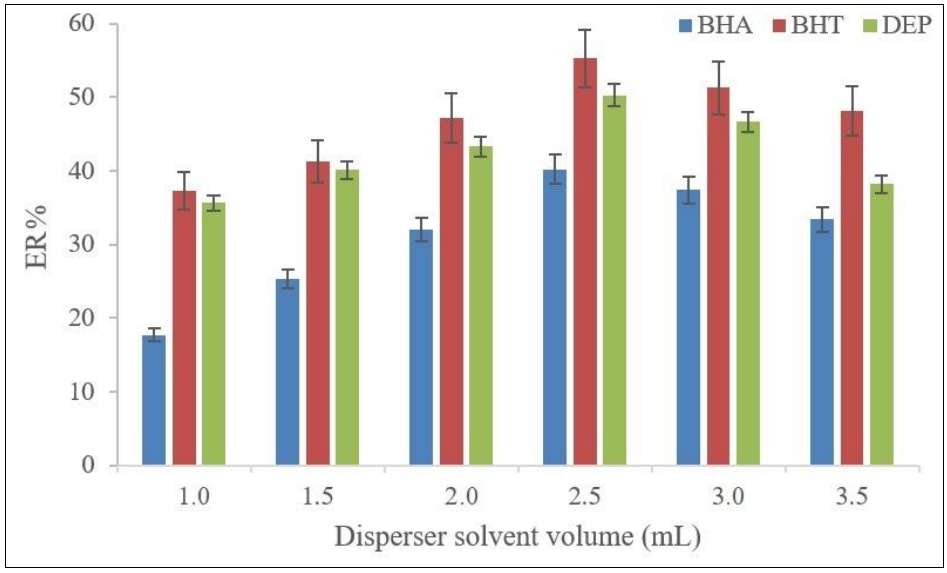


Fig. 4. Effect of the disperser solvent volume on the ER. Extraction conditions are the same as those used in Fig. 3, except that 2-propanol was used as the disperser solvent.

increase as the disperser solvent volume increases up to 2.5 ml and then dwindle. This is due to the low volumes of the disperser solvent (less than 2.5 ml), the effective dispersion of the extraction solvent is not achievable. Also using high volumes of the disperser solvent (more than 2.5 ml) reduces the polarity of the aqueous solution and results in high solubility of the analytes in the aqueous phase. This phenomenon reduces the partition coefficients of the target compounds between the aqueous phase and organic phase which eventually leads to low ERs.

Accordingly, 2.5 ml of 2-propanol was opted as the optimum volume for the disperser solvent.

Study of Ionic Strength

Typically, adding salt in an aqueous phase decreases the solubility of the analytes in it and increases their distribution into an organic phase which results in an increase in the ERs of the target compounds. Moreover, adding the salt more than the optimum amount will enhance the viscosity of the aqueous phase and eventually dwindles the extraction efficiency. Therefore, selection of a proper salt and its optimum concentration are of great importance. In order to select the salt type, various salts including NaCl, Na_2SO_4 and $NaNO_3$ were tested (2.5%, *w/v*, of each salt) with utilizing 100, 90 and 95 µl of the extraction solvent, respectively. Other parameters were kept constant. According to the output of the experiments, using Na_2SO_4 resulted in better ERs in comparison to other salts. This can be due to the bivalent anion of Na_2SO_4 which increases the ionic strength more than the monovalent anions *e.g.* Cl^- and NO_3^-. Thus, Na_2SO_4 was chosen as the optimum salt type.

After the assessment of the optimum salt type, the effect of the concentration of Na_2SO_4 (ionic strength) was evaluated in the range of 0-10%, *w/v*. Other conditions, except the extraction solvent volume, were kept constant. To obtain a similar volume of the sedimented phase, (10 ± 0.5 µl), the analysis was performed using various volumes of the extraction solvent (104, 90, 85, 81 and 73 µl of the extraction solvent for 0, 2.5, 5.0, 7.5 and 10%, *w/v*, of Na_2SO_4, respectively). Obtained results (Fig. 5) demonstrate that the ERs of the target compounds enhance by enhancing the concentration of the salt up to 2.5% (*w/v*) and then dwindle by increasing the excess amounts of Na_2SO_4 which is due to the enhancement in viscosity of the aqueous phase. This phenomenon results in the diminution of mass transfer of the analytes. Hence, 2.5% (*w/v*) Na_2SO_4 was utilized in the next experiments.

Optimization of the Extraction Solvent Volume

As a matter of fact, the volume of extraction solvent plays a significant role on EFs, ERs, and limits of detection (LODs) and quantification (LOQs) of the analytes. In order to evaluate the optimum extraction solvent volume, different volumes were surveyed in the range of 90-120 µl. The obtained data illustrated that the ERs enhanced as the extraction solvent volume increased, however, the EFs diminished (Fig. 6). The decline of EFs is considered as a result of the dilution effect. It is worth noting that by using less than 90 µl volumes, the sedimented organic phase volume was so low and irreproducible that its collection and handling were very arduous. Based on the results, in 90 µl of the extraction solvent, the EFs of the analytes were high, and low LODs were achievable in this volume. Therefore, 90 µl of the extraction solvent was opted as the optimum extraction solvent volume.

Study of Solution pH

In order to have an all-embracing investigation on the extraction efficiency of the target compounds, the effect of aqueous solution pH was also evaluated. Different experiments were done with adjusting the aqueous solution pH in the range of 2-12 by means of 1 M HCl or NaOH solution. All previous conditions of the analysis were fixed. The results illustrated that at highly acidic or alkaline pHs, the ERs of the analytes were decreased. This decrease could be attributed to the decomposition or conformation of the analytes to ionic forms leading to enhance their solubility in water and decrease their affinity for migration into the extraction solvent. Considering that the pHs of all evaluated samples were between 6 and 8, there is no need for pH adjustment in this study and the experiments were fulfilled without pH adjustment.

Study of Centrifuging Time and Rate

Centrifugation step is prominent in separating the extraction solvent from the aqueous phase. The rate and time of centrifugation were studied in the ranges of 2000-5000 rpm and 2-7 min, respectively. According to the results obtained from the experiments, 3000 rpm and 5 min were opted as the optimum rate and time of centrifugation, respectively. It is worthwhile to mention that at speeds and times lower than 3000 rpm and 5 min, the solutions were still turbid and the phase separation was imperfect. So, the ERs were decreased. Moreover, it was observed that the centrifuge times and rates higher than 3000 rpm and 5 min, respectively, had no significant effect on the ERs of the analytes.

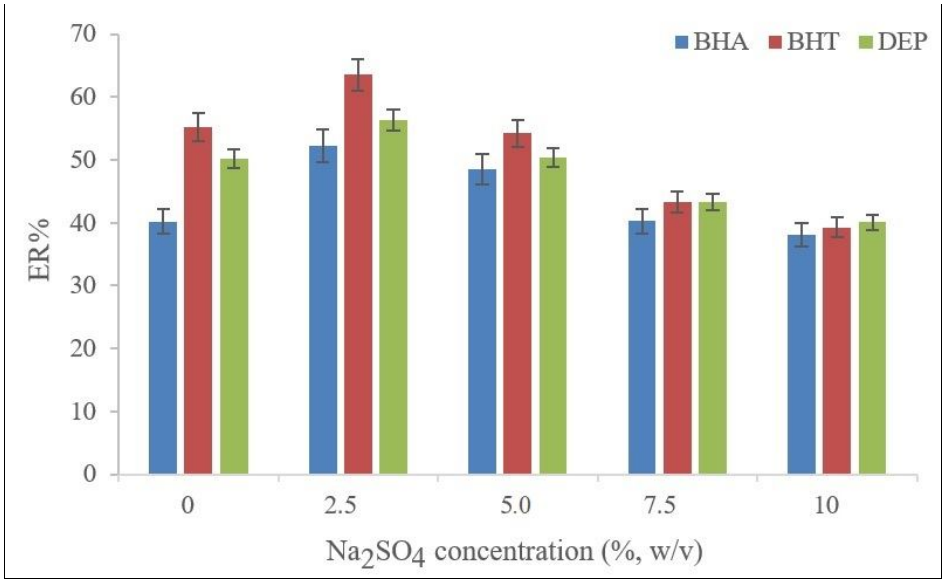


Fig. 5. Effect of Na_2SO_4 concentration on the ER. Extraction conditions are the same as those used in Fig. 4, except that 2.5 ml of 2-propanol and Na_2SO_4 were utilized as the disperser solvent and salting out agent, respectively.

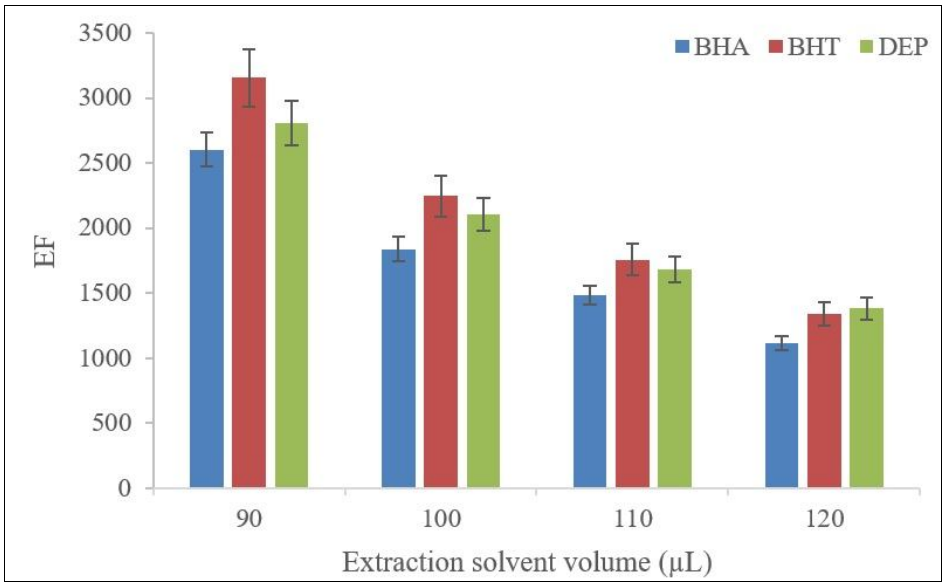


Fig. 6. Effect of the extraction solvent volume on the EF. Extraction conditions are the same as those used in Fig. 5, except that 2.5%, *w/v*, Na_2SO_4 was utilized.

Validation of the Method

Analytical figures of merit such as LOD, LOQ, linear range (LR), ER, EF, RSD and correlation coefficient (r^2) were calculated under the above-mentioned optimized conditions. The obtained data are listed in Table 2. It is noted that after the establishment of the method, it was applied on all real samples and the sedimented phase was injected into GC-MS. It was found that in all samples at

Table 2. Quantitative Features of the Proposed Method for the Analytes

Analyte	LOD[a]	LOQ[b]	LR[c]	Calibration curve equation	r^{2}[d]	RSD (%)[e]		EF ± SD[f]	ER ± SD[g]
						Intra-day	Inter-days		
BHA	0.22	0.74	0.74-1000	A = 63.24C + 76.35[h]	0.997	5.0, 4.7, 4.5	6.4, 5.9, 5.2	2600 ± 200	52 ± 4
BHT	0.18	0.61	0.61-1000	A = 363.73C + 107.43	0.996	4.1, 3.5, 3.2	5.3, 4.8, 4.0	3150 ± 250	63 ± 5
DEP	0.23	0.77	0.77-1000	A = 322.48C + 222.27	0.999	3.9, 3.2, 3.2	4.0, 3.9, 3.9	2800 ± 150	56 ± 3
DBP	0.21	0.71	0.71-1000	A = 402.35C + 851.21	0.991	6.1, 6.1, 5.2	7.2, 7.2, 6.8	2950 ± 200	59 ± 4
DIBP	0.19	0.65	0.65-1000	A = 389.23C + 137.71	0.994	5.7, 5.5, 5.0	6.9, 6.4, 6.0	2900 ± 200	58 ± 4
BPA	0.24	0.80	0.80-1000	A = 383.25C + 582.31	0.999	5.0, 4.4, 4.1	6.5, 6.1, 5.7	2700 ± 150	54 ± 3
p-Xylene	0.38	1.26	1.26-1000	A = 285.85C - 97.61	0.992	5.1, 4.2, 4.1	5.9, 5.9, 5.7	3050 ± 150	61 ± 3

[a]Limit of detection (S/N = 3) (µg l^{-1}). [b]Limit of quantification (S/N = 10) (µg l^{-1}). [c]Linear range (µg l^{-1}). [d]Correlation coefficient. [e]Relative standard deviation (n = 6, C= 10, 20 and 50 µg l^{-1} of each analyte, respectively, from left to right) for intra- and (n = 4, C = 10, 20 and 50 µg l^{-1} of each analyte, respectively, from left to right) for inter-day precisions. [f]Enrichment factor ± standard deviation (n = 3, C = 0.5 mg l^{-1} of each analyte). [g]Extraction recovery ± standard deviation (n = 3, C= 0.5 mg l^{-1} of each analyte). [h]A = peak area and C = concentration (µg l^{-1}).

least two compounds from seven compounds (BHA, BHT, DEP, DBP, DIBP, BPA and *p*-xylene) were detected. Therefore analytical characteristics of the method were obtained for the seven compounds mentioned above. The data demonstrate wide LRs and good linearity ($r^2 \geq 0.991$) for the target compounds. The LODs, based on a signal-to-noise ratio of 3, and the LOQs based on a signal-to-noise ratio of 10, were achieved in the ranges of 0.18-0.38 and 0.61-1.26 µg l^{-1}, respectively. The repeatability, illustrated as RSD, was computed by analyzing 10, 20 and 50 µg l^{-1} standard solutions with respect to each analyte. The obtained RSDs% were in the ranges of 3.2-6.1% for intra-day (n = 6) and 3.9-7.2% for inter-day (n = 4) precisions. The ERs and EFs for the target compounds at a concentration of 0.5 mg l^{-1} of each analyte were calculated to be in the ranges of 52-63% and 2600-3150, respectively. Low LODs and LOQs, high EFs, wide LRs, and good repeatability are the main preferences of the mentioned method for analyzing the target compounds.

Analysis of Real Samples

Applicability of the suggested method to real samples was investigated by analyzing various samples stored in plastic containers like mineral waters, carbonated soft

Table 3. Chronological Study of the Concentration of the Target Compounds in Different Storage Conditions of Three Brands of Mineral Water

Mean concentration of the target compounds (µg l^{-1}) ± standard deviation (n = 3)																		
	Stored at room temperature						Stored in a refrigerator (4 °C)						Stored in a freezer (-20 °C)					
Storage days→	1	2	5	10	30	60	1	2	5	10	30	60	1	2	5	10	30	60
									Analyte									Mineral water A
BHA	ND [a]	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
BHT	0.64	0.90	0.91	1.11	1.97	2.23	0.71	0.70	0.70	0.92	1.82	2.13	ND	ND	ND	ND	ND	ND
	±0.02	±0.03	±0.03	±0.03	±0.06	±0.07	±0.02	±0.02	±0.02	±0.03	±0.06	±0.07						
DEP	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
DBP	1.07	1.51	2.08	2.63	4.17	4.62	0.78	0.81	1.14	2.21	3.98	4.36	NQ [b]	NQ	0.74	1.02	1.71	1.74
	±0.06	±0.09	±0.12	±0.15	±0.25	±0.27	±0.04	±0.03	±0.06	±0.13	±0.19	±0.26			±0.02	±0.05	±0.10	±0.08
DIBP	4.51	4.51	4.70	4.96	6.05	6.83	3.70	4.11	4.52	4.71	6.00	6.58	1.81	1.81	2.02	2.17	3.39	3.65
	±0.24	±0.21	±0.22	±0.19	±0.33	±0.31	±0.19	±0.21	±0.20	±0.22	±0.32	±0.33	±0.08	±0.08	±0.10	±0.09	±0.18	±0.17
BPA	0.82	0.82	0.85	0.85	0.88	0.96	0.82	0.83	0.83	0.86	0.86	0.86	0.83	0.83	0.85	0.85	0.85	0.85
	±0.02	±0.02	±0.02	±0.02	±0.02	±0.04	±0.02	±0.03	±0.02	±0.03	±0.02	±0.02	±0.02	±0.03	±0.02	±0.03	±0.03	±0.03
p-Xylene	4.11	4.61	5.01	5.04	5.12	6.63	5.01	5.11	5.71	5.15	5.11	5.66	4.06	4.06	5.11	5.27	5.05	5.01
	±0.17	±0.17	±0.20	±0.21	±0.21	±0.26	±0.20	±0.21	±0.22	±0.21	±0.19	±0.23	±0.16	±0.15	±0.17	±0.14	±0.18	±0.21
									Mineral water B									
BHA	3.00	3.02	3.28	4.03	6.04	9.68	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	±0.13	±0.15	±0.13	±0.14	±0.28	±0.29												
BHT	0.74	0.74	0.75	0.81	1.10	1.60	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	±0.02	±0.02	±0.02	±0.02	±0.03	±0.05												
DEP	NQ	NQ	NQ	NQ	0.79	0.85	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
					±0.02	±0.01												
DBP	0.90	0.90	1.20	2.00	2.90	4.57	1.00	1.00	1.28	2.22	3.14	4.55	NQ	0.80	0.97	1.70	2.41	4.47
	±0.05	±0.04	±0.07	±0.12	±0.14	±0.26	±0.06	±0.05	±0.05	±0.12	±0.18	±0.27		±0.04	±0.05	±0.10	±0.12	±0.25
DIBP	2.05	2.64	2.92	3.61	4.29	7.22	NQ	2.21	2.80	3.62	4.00	7.18	NQ	NQ	2.10	3.50	4.14	7.14
	±0.11	±0.10	±0.15	±0.19	±0.22	±0.31		±0.11	±0.14	±0.17	±0.19	±0.39			±0.09	±0.15	±0.20	±0.36
BPA	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
p-Xylene	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
									Mineral water C									
BHA	0.80	0.80	0.87	0.91	1.23	1.56	NQ	NQ	0.80	0.84	1.00	1.22	NQ	NQ	NQ	NQ	0.80	0.85
	±0.03	±0.02	±0.04	±0.04	±0.05	±0.06			±0.02	±0.03	±0.04	±0.05					±0.03	±0.02
BHT	NQ	NQ	0.68	0.68	0.70	1.03	NQ	NQ	NQ	NQ	0.71	0.80	NQ	NQ	NQ	NQ	NQ	0.68
			±0.02	±0.02	±0.03	±0.03					±0.02	±0.02						±0.02
DEP	NQ	NQ	NQ	NQ	NQ	0.80	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
						±0.02												
DBP	3.57	3.71	3.98	4.12	5.07	5.71	1.08	1.08	1.97	2.07	3.61	4.35	3.12	3.14	3.72	4.01	4.86	5.96
	±0.21	±0.19	±0.23	±0.24	±0.25	±0.31	±0.06	±0.05	±0.07	±0.08	±0.21	±0.25	±0.19	±0.18	±0.22	±0.24	±0.29	±0.26
DIBP	5.72	5.72	5.81	6.03	7.81	8.79	2.49	2.78	3.36	4.09	5.02	5.16	NQ	1.74	2.12	4.14	6.51	7.02
	±0.31	±0.26	±0.25	±032	±0.30	±0.45	±0.10	±0.10	±0.15	±0.19	±0.26	±0.22		±0.09	±0.11	±0.22	±0.33	±0.36
BPA	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
p-Xylene	5.12	4.90	5.04	6.78	7.21	7.06	4.81	5.01	5.90	6.06	5.09	5.21	5.04	5.07	5.05	5.39	5.12	5.13
	±0.21	±0.18	±0.17	±0.28	±0.30	±0.29	±0.17	±0.19	±0.21	±0.24	±0.18	±0.21	±0.20	±0.21	±0.20	±0.20	±0.17	±0.16

[a]Not detected. [b]Not quantified (LOD < the obtained concentration < LOQ).

Table 4. Concentrations of the Target Compounds in the Studied Drinks and Liquids

Analyte	Mean concentration of the target compounds (μg l^{-1}) ± standard deviation (n = 3)					
	Sterile distilled water	Physiological serum A	Physiological serum B	Carbonated soft drink A	Carbonated soft drink B	Yogurt drink
BHA	ND [a]	ND	ND	ND	ND	ND
BHT	ND	ND	ND	ND	ND	ND
DEP	ND	ND	ND	8.75 ± 0.26	4.57 ± 0.14	ND
DBP	6.40 ± 0.35	7.84 ± 0.45	6.34 ± 0.32	15.4 ± 0.91	9.08 ± 0.54	1.47 ± 0.06
DIBP	11.4 ± 0.61	8.89 ± 0.44	10.1 ± 0.55	ND	15.7 ± 0.81	ND
BPA	9.1 ± 0.39	ND	4.12 ± 0.16	21.3 ± 0.92	ND	15.3 ± 0.66
p-Xylene	ND	ND	ND	ND	ND	ND

[a]Not detected.

Table 5. Study of Matrix Effect in the Samples Spiked at Different Concentrations. Analytes' Contents were Subtracted. All Samples were Used without Dilution, Except Carbonated Soft Drinks A and B, and Yogurt Drink which were diluted at the Ratios of 1:2, 1:4, and 1:4, Respectively

Analyte	Mean relative recovery ± standard deviation (n = 3)								
	Mineral water A	Mineral water B	Mineral water C	Sterile distilled water	Physiological serum A	Physiological serum B	Carbonated soft drink A	Carbonated soft drink B	Yogurt drink
	All samples were spiked with each analyte at a concentration of 20 μg l^{-1}								
BHA	90 ± 2	95 ± 2	98 ± 3	88 ± 1	99 ± 2	83 ± 1	99 ± 2	84 ± 2	109 ± 2
BHT	93 ± 1	103 ± 3	89 ± 2	85 ± 2	106 ± 3	91 ± 2	88 ± 1	82 ± 3	111 ± 3
DEP	95 ± 2	100 ± 4	93 ± 4	90 ± 4	101 ± 2	87 ± 3	90 ± 3	95 ± 3	89 ± 3
DBP	96 ± 3	98 ± 3	91 ± 3	91 ± 3	95 ± 1	85 ± 1	93 ± 2	90 ± 1	90 ± 4
DIBP	94 ± 4	105 ± 1	94 ± 1	93 ± 2	91 ± 2	82 ± 3	95 ± 1	86 ± 3	92 ± 2
BPA	93 ± 2	91 ± 3	90 ± 1	97 ± 2	94 ± 4	92 ± 2	85 ± 1	87 ± 3	90 ± 2
p-Xylene	91 ± 1	97 ± 3	91 ± 3	87 ± 2	90 ± 4	89 ± 2	90 ± 4	85 ± 2	90 ± 3
	All samples were spiked with each analyte at a concentration of 40 μg l^{-1}								
BHA	88 ± 1	99 ± 3	101 ± 4	93 ± 2	101 ± 2	80 ± 1	102 ± 2	80 ± 2	103 ± 3
BHT	90 ± 3	96 ± 3	93 ± 1	87 ± 2	105 ± 4	86 ± 2	92 ± 3	84 ± 4	102 ± 1
DEP	96 ± 2	95 ± 1	90 ± 2	95 ± 3	96 ± 3	92 ± 1	93 ± 2	92 ± 2	92 ± 2
DBP	90 ± 4	95 ± 2	85 ± 2	92 ± 1	92 ± 2	95 ± 1	95 ± 2	95 ± 3	95 ± 3
DIBP	88 ± 2	102 ± 2	93 ± 3	93 ± 3	91 ± 4	85 ± 3	90 ± 1	90 ± 1	89 ± 2
BPA	90 ± 2	88 ± 3	93 ± 1	91 ± 2	93 ± 3	90 ± 2	82 ± 3	84 ± 2	88 ± 2
p-Xylene	93 ± 2	107 ± 2	85 ± 4	81 ± 2	86 ± 3	93 ± 4	84 ± 3	91 ± 2	94 ± 3

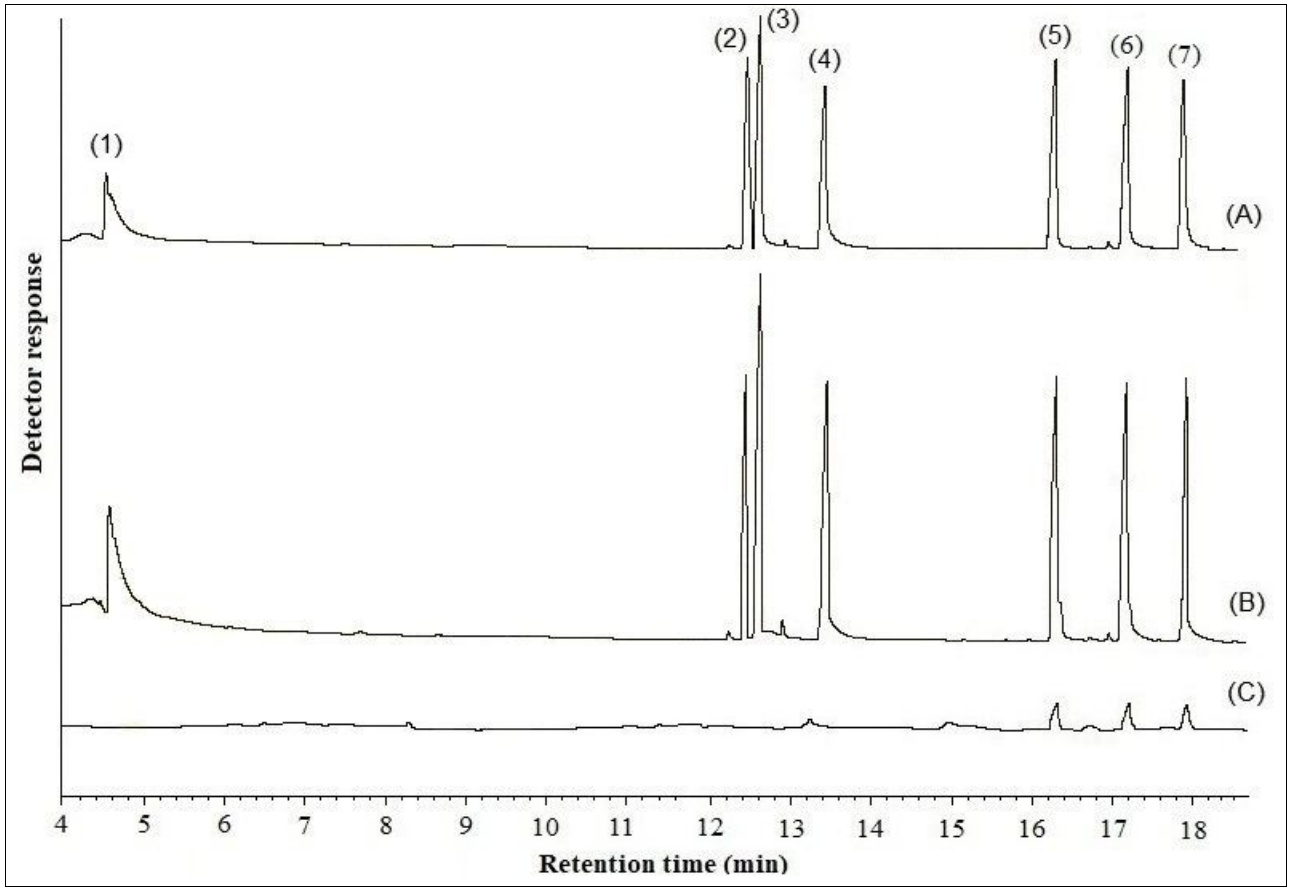


Fig. 7. Typical GC-FID chromatograms of: (A) standard solution (1000 mg l^{-1} in methanol, each analyte, except *p*-xylene which its concentration was 100 mg l^{-1}), (B) deionized water spiked with 0.5 mg l^{-1} of each analyte, and (C) sterile distilled water after performing the proposed method, except chromatogram A in which direct injection without preconcentration was done. Peaks identification: (1) *p*-xylene; (2) BHA; (3) BHT; (4) DEP; (5) DIBP; (6) DBP; and (7) BPA.

drinks, yogurt drink, physiological serum, and sterile distilled water under the above-mentioned optimum conditions. In order to have an accurate identification, the samples were injected into GC-MS after performing the microextraction procedure. In all mineral waters, DBP, DIBP and BHT were found. In two mineral water samples, BHA, DEP, and *p*-xylene were also detected. BPA was recognized in one mineral water sample. In the other samples, the following compounds were detected: sterile distilled water, DBP, DIBP and BPA; physiological serum A, DBP and DIBP; physiological serum B, DBP, DIBP and BPA; carbonated soft drink A, DEP, DBP and BPA; carbonated soft drink B, DEP, DBP and DIBP; and yogurt drink, DBP and BPA. The concentrations of the analytes in the chronologically studied mineral water samples and the other plastic-stored samples were determined using GC-FID data and are presented in Tables 3 and 4, respectively. It is obvious from Table 3 that the storage time and temperature are important parameters in releasing the analytes into the mineral waters. In all cases by increasing the storage time, the concentrations of the compounds of interest were enhanced in the mineral water samples. On the other hand, storage at low temperature is favorable in most cases. Figure 7 depicts the typical GC-FID chromatograms for direct injection of a standard solution, and the enriched analytes in the sedimented phases obtained from deionized

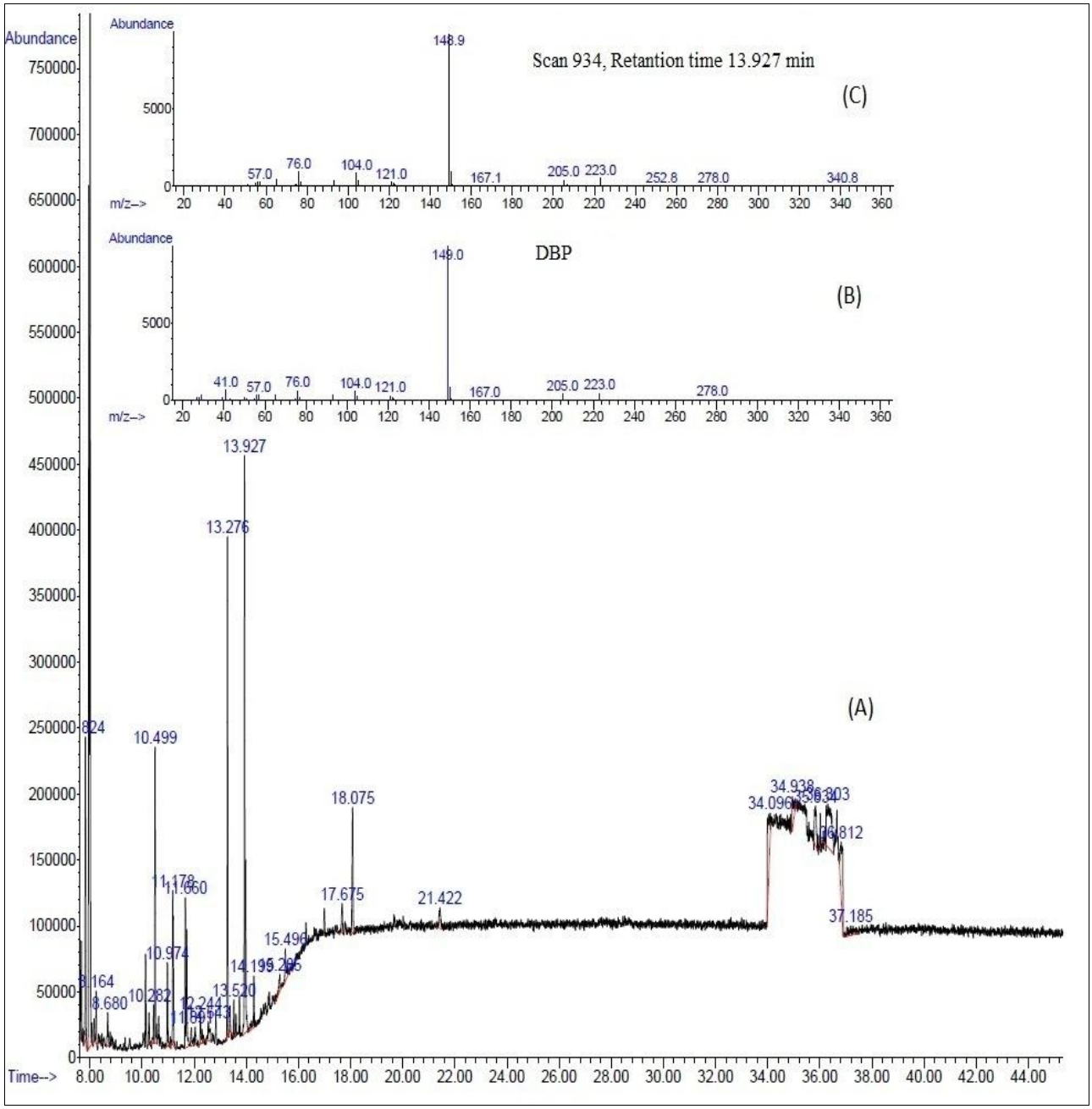


Fig. 8. Typical GC-TIC-MS chromatogram of the physiological serum after performing the proposed method (A), the mass spectrum of DBP (B), and scan 934 (retention time 13.927 min) (C).

water containing 0.5 mg l^{-1} of each target compound and sterile distilled water. The typical GC-total ions current (TIC)-MS chromatogram obtained for the physiological serum and the related mass data are given in Fig. 8. For instance, the presence of DBP in the physiological serum was authenticated by comparing the mass data for scan 934 (retention time 13.927 min) with those of the studied analyte. In order to investigate the method accuracy and

Table 6. Comparison of the Applied Method with other Methods Used in Preconcentration and Determination of the Target compounds

Method	Sample	LOD[a]	LOQ[b]	LR[c]	RSD (%)[d]	EF[e]	Ref.
SPE-GC-MS[f]	Water samples	0.0015	0.0051	5-200	6.9	-	[41]
SPE-UPLC-MS-MS[g]	Human milk	0.09	0.40	0.40-6.40	15	-	[42]
DLLME-GC-FID[h]	Cow milk	1.5-3.0	2.5-11	10-1000	3-4	397-499	[43]
SPME-GC-MS[i]	Tap water	0.007-0.02	-	0.02-10	10-17	-	[44]
DLLME-GC-FID	Different drinks and liquids	0.18-0.38	0.61-1.26	0.61-1000	3.2-6.1	2600-3150	Present method

[a]Limit of detection (µg l^{-1}). [b]Limit of quantification (µg l^{-1}). [c]Linear range. [d]Relative standard deviation. [e]Enrichment factor [f]Solid phase extraction-gas chromatography-mass spectrometry. [g]Solid phase extraction-ultra performance liquid chromatography-mass spectrometry-mass spectrometry. [h]Dispersive liquid-liquid microextraction-gas chromatography-flame ionization detection. [i]Solid phase microextraction-gas chromatography-mass spectrometry.

matrix effect in the evaluated samples, an added-found method was applied. For this purpose, the evaluated samples and deionized water were spiked at the same concentrations (20 and 40 µg l^{-1} of each analyte). Subsequently, the proposed method was performed on them to calculate the relative recoveries in real samples compared to deionized water. As it is obvious in Table 5, real samples' matrices do not have any prominent effect on the microextraction approach and can be utilized as an appropriate method to analyze the target compounds in the mentioned samples. It is worthwhile to mention that the carbonated soft drinks A and B, and yogurt drink samples were diluted with deionized water before performing the method at ratios of 1:2, 1:4, and 1:4, respectively. Other samples were analyzed without any dilution.

Comparison of the Applied Method with other Methods

The analytical figures of merit of the applied method for the analysis of the target compounds were compared with the previously reported methods and summarized in Table 6. It is clear that RSDs% of the developed method are comparable or better than those of the other works. This method also presents wider LRs in comparison with other methods. The LODs and LOQs of the method are comparable or better than those of the other mentioned methods, except in the cases in which MS has been used as the detection system that is inherently more sensitive than FID. The EFs obtained from the applied method are higher than the EFs of the other method.

CONCLUSIONS

In the present research, a DLLME procedure was applied for the extraction and preconcentration of the unwanted and migrated compounds from plastic containers into different liquids and drinks prior to their detection and quantification by GC-MS and GC-FID. Applying the proposed method successfully disclosed the presence of some analytes in the studied samples. These analytes are hazardous and can cause a great risk for human health. The obtained experimental data illustrated that the applied method has various preferences such as no matrix effect, ease of operation, low RSDs, elevated EFs and the usage of

little toxic solvents. The obtained data demonstrated that the suggested procedure can be applied as an efficient approach for the preconcentration and microextraction of the analytes from various drinks and liquids and fulfill the food control process carefully. Also, the obtained results proved that the plastic containers are not inert and contaminate the drinks stored in them, so it should be considered as a potential risk for human health and their applications must be limited.

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