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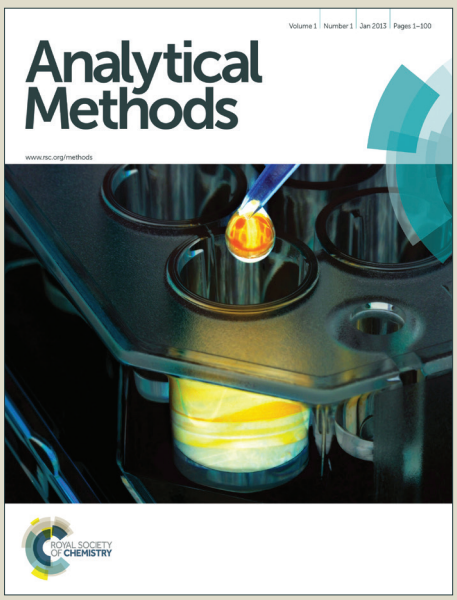

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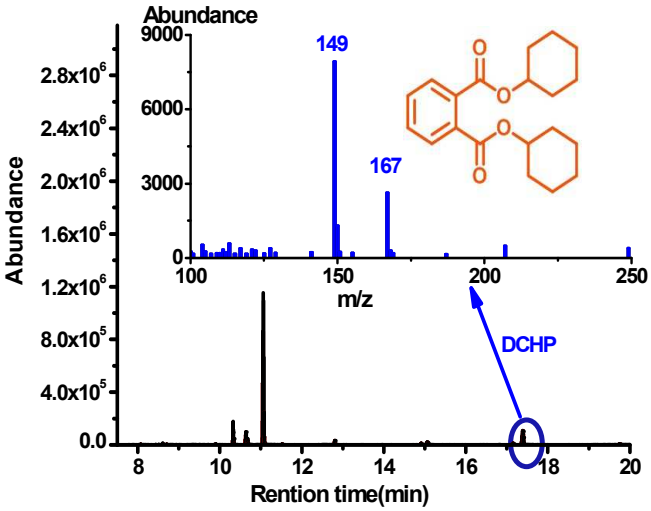

Eight kinds of PAEs in five different brands of soybean milks were successfully determined using DLLME method coupled with GC-MS.

Determination of phthalate acid esters in soybean milks using dispersive liquid-liquid microextraction coupled with gas chromatography and mass spectrometric detection

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Abstract

Dispersive liquid–liquid microextraction (DLLME) was coupled with gas chromatography and mass spectrometric detection for the determination of eight phthalate acid esters (PAEs) in soybean milks. Parameters impacting on the extraction efficiencies were optimized including organic solvents to extract PAEs from soybean milks, salt concentrations and organic solvents for DLLME. Under the optimal condition, limits of detection (LODs) and limits of quantification (LOQs) were in the range of 0.57—0.79 and 1.90—2.63 ngg^{-1}, respectively. Linearities varied in the range of 1—16000 ngg^{-1} with the correlation coefficients of 0.9993–0.9998. The precisions of the method were 2.9–3.2 in terms of RSD% based on triplicate measurements. The preconcentration factors were in the range of 200-260. The recoveries of eight PAEs were in the range from 79.0 to 110% at three spiked levels. The trace PAEs in five different brands of soybean milks purchased from the market were determined successfully.

Keywords: Dispersive liquid–liquid microextraction; Gas chromatography and mass spectrometric detection; Phthalate acid esters; Soya-bean milk

Introduction

Soybean milk is a beverage made from soybeans and originated from China. Many people consider soybean milk to be an everyday beverage because of its low price, high content of proteins, antioxidants, unsaturated fatty acids, dietary fibers and no cholesterol, etc. Soybean milk consumption has gained popularity in many Asian countries and is also spreading to many other countries as well. Thus, soybean milk packing is inevitably required for transportation and storage. Even though pure polyvinyl chloride (PVC) is fairly unstable, the manifold applications are made possible by the discovery of effective additives for the polymer. The most important additives for the processing of PVC are phthalic acid esters (PAEs), which may be incorporated into the polymer to improve flexibility, workability and general handling properties.[1] Due to its particularly good polymer characteristics, PVC has an enormously wide spectrum of applications for packaging liquid products, such as beverages, edible oils, detergents, cosmetics and pharmaceuticals.

The source of PAEs in food is attributed mainly to (i) compounds which are directly present in the aquifer as contaminants; (ii)external contamination from the bottling plant and (iii) migration from containers, especially during storage.[2-5] There were several reports discussed the migration of PAEs from plastics into food.[6-8] The amount of PAEs in packaged foods depends on many factors including the concentration of PAEs in the packaging material or printing ink, the storage period, the storage temperature, the fat content in the food and the contact area.[1] In May, 2011, a scandal in Taiwan concerning food contamination with PAEs received worldwide attention. Then, Public concern about PAEs in food is overwhelming, and food contamination with PAEs has been regarding as a research priority to provide urgently needed information for proper interventions in China.[9] Toxicities of PAEs could be cardiotoxicity, hepatotoxicity and nephrotoxicity.[10]

Soybean milks have complex sample matrices. They contain in general high concentration of proteins, carbohydrates, fatty acids, dietary fibers and relative low concentration of PAEs. An extraction process is necessary in the determination of PAEs prior to performing chromatographic analysis. Extraction has two functions. One is to enrich the low concentration of analytes to adequate level for detection or

quantification; the other is to isolate the desired analytes from sample matrices which the instruments cannot detect directly. In principle, either liquid-liquid extraction (LLE) or solid phase extraction (SPE) may be applied. However, none of them is ideal in practice. LLE is a time consuming and tedious process, and requires a large amount of expensive and high-purity organic solvents. After LLE, it usually requires evaporation of the large volume solvents which are often flammable and hazardous to human and environment. When subjected to SPE, a sample with complex matrix, such as soybean milk, may plug into sorbent pores. Although pre-filtrating the samples can avoid clogging and cleaning of SPE, it possibly leads to the losses and contamination of the analytes.[11, 12] In recent years, solid-phase microextraction(SPME)[13-15] and liquid-phase microextraction (LPME)[16, 17] had been developed as a solvent-minimized sample pretreatment procedure, in which the analytes are extracted from aqueous or gaseous samples on to a solid porous hollow fiber/membrane/fused silica fiber coated with a stationary phase. SPME has important advantages over conventional extraction techniques, because it is solvent free, fast, portable and easy to use. But SPME also suffers from some drawbacks such as fiber fragile, limited lifetime and sample difficult to carryover, etc[18, 19]. For LPME, it overcomes the drawbacks of SPME and has the characteristics of simple setup, fast processing and low-cost, etc., but still leaves some disadvantages: fast stirring would tend to form air bubbles[20] and equilibrium cannot be attained within the time required in most cases [21]. Recently, Assadi and co-workers[22] have developed a novel microextraction technique called dispersive liquid–liquid microextraction (DLLME). DLLME is based on the appropriate mixture of a water-immiscible solvent (extractant) and a water-miscible solvent (disperser), which is rapidly injected into the aqueous sample that contains the analytes. After formation of a cloudy solution with a wide contact surface between the sample and extracted agent, droplets of the water-immiscible solvent containing the analytes are obtained. Through centrifugation, the droplets of the water-immiscible solvent containing the analytes can be collected in the sedimented phase and determined by chromatography or spectrometry methods. Therefore, DLLME is fast, inexpensive, easy to operate with a high enrichment factor and consumes low volume of organic solvent. Till now, DLLME method has been applied for the extraction a large variety of organic compounds[23]

and metal ions[24] from various kinds of matrices including PAEs in water[25], cow milk[26, 27] and recently in wine[28]. However, no report has been made on the determination of PAEs in soybean milks.

The goal of this work is to develop a reliable and rapid method for the determination of PAEs in soybean milks. It was accomplished by employing DLLME for sample pretreatment, gas chromatography for separation and mass spectrometry for detection. Different experimental parameters were optimized to maximize extraction efficiency. Under the optimal conditions, eight PAEs in five brands of soybean milks from the local markets were determined successfully.

Experimental section

Chemicals and solutions

All chemicals mentioned in this section were obtained from Aladdin reagent (Shanghai, China). Common phthalic acid esters (PAEs) included dimethyl phthalate (DMP), diethyl phthalate (DEP), diisobutyl phthalate (DIBP), dibutyl phthalate (DBP), dipentyl phthalate (DPP), dicyclohexyl phthalate (DCHP), di(2-ethylhexyl)phthalate (DEHP) and dioctyl phthalate (DNOP). Carbon tetrachloride, 1,1,1-trichloroethane (1,1,1-TCE), tetrachloroethylene and chlorobenzene were tested as the extractact in DLLME. Methanol, ethanol, acetonitrile, acetone, isopropanol and tetrahydrofuran were tested as the extraction solvent for the extraction of PAEs from soybean milks and also as disperser in DLLME.

The stock solutions of eight PAEs were prepared in methanol at a concentration of 0.4 mgg^{-1}. The stock solutions were stored at 4 ℃ in a refrigerator when not in use. The working standard solutions were prepared by appropriately diluting the stock solution of PAEs with ultrapure water as needed.

Five kinds of soybean milks in polyvinyl chloride (PVC) packing and produced by different companies were purchased from local supermarkets (Shanghai, China).

Instrumentation

Analysis of PAEs was carried out on an Agilent 7890 gas chromatograph (GC) with a 5975C Triple-Axis Detector (Agilent Technologies, CA, USA). The mass spectrometric detection （MS） was operated at the electron impact (EI) mode (70

eV). The Agilent 7890 gas chromatograph was equipped with a split/splitless injector. Helium (99.999%) was used as carrier gas at a constant flow rate of 1 mL/min. PAEs were separated on a HP-5 capillary column (5% phenyl, 95% methyl siloxane, 30 m x 0.32 mm i.d. x 0.25 μm film thickness) (Agilent Technologies, CA, USA) with the following oven temperature programming: initial temperature: 60 ℃ (held for 1 min) and increased to 220 ℃ at a rate of 20 ℃/min and held 220 ℃ for 1 min and then from 220 to 280 ℃ at a rate of 5 ℃/min and held at 290 ℃ for 4 min. Injector temperature was set at 300 ℃. The EI ion source and interface temperature were 230 and 280 ℃, respectively. The solvent delay time was 8 min. All injections were in splitless mode. The MS was operated on the total ion current (TIC) mode, scanning from m/z 50 to 550 for identification purposes. To gain the highest possible sensitivity, selective ion monitoring (SIM) mode was adopted for quantitative determination of the PAEs. For each compound, the ion for quantitative analysis was based on selection of the highest intensity mass peak. Peaks of m/z 163 and/or 149 were scanned.

Procedure of the extraction of PAEs from soybean milk

All the extraction apparatus were glass-made, washed with methanol and dried with air before use.

The extraction of PAEs could be divided into two steps. In the first step, 5 mL of soybean milk was placed in a 10 mL glass tube. After spiking the standard solution of PAEs, appropriate amount of sodium chloride was added. The glass tube was manually shaken to dissolve the salt; then, 3 mL extraction organic solvent (used as disperser in the next step) was added and centrifuged at a rate of 4000 rpm for 5 min, and PAEs were extracted into the upper organic phase.

In the second step, 5 mL ultrapure water was placed into a 10 mL glass tube with conical tip at the bottom, and 1 mL of the upper organic phase obtained in the first step was added to the glass tube with conical tip; then, 40 μL carbon tetrachloride was injected rapidly into this mixture, and centrifuged for 5 min at 4000 rpm to obtain the sedimented phase; finally, 1 μL of the sedimented phase was removed and injected into the GC system.

Result and discussion

In this two-step extraction process, optimization of the first step cannot be performed independently from the second step. The organic solvent used as extractant in the first step acts as the disperser in the second step. The solvent properties, dispersive properties and volume would be more critical to the total extraction efficiencies. Optimization of the two step processes is more complex than the guidelines proposed for the optimization of a typical DLLME.

Optimization of parameters in the extraction of PAEs from Soybean milks

Selection of extraction solvent

The extraction solvent was not only used as the extraction solvent which could extract of PAEs from soybean milks but also as the disperser for the following DLLME step. There are several requirements to select the extraction solvent: (i) the solvent is capable of extraction of PAEs from the soybean milks, (ii) the solvent can be miscible with the aqueous phase. The experiments were performed by adding different kinds of organic solvents which were methanol, ethanol, acetonitrile (ACN), acetone, isopropanol and tetrahydrofuran, and only ACN was observed to form a two phase system. Thus, ACN was chosen as the extraction solvent for the following work.

Study of ACN volume

To evaluate the influence of ACN volume, 1, 2, 3, 4 and 5 mL of ACN were separately added into the soybean milks containing 0.5 g NaCl, and two phases were only observed for 3, 4 and 5 mL ACN added with the organic phase volumes of 1.2, 2.6, and 3.4 mL, respectively. As it can be seen from Fig.1, with the increase of ACN volume, the PAEs were diluted into the ACN phase, and the peak areas decreased relatively. The optimum volume for the extraction of PAEs from soya-bean milk samples is 3 mL ACN, and 3 mL ACN was chosen as the optimum volume for the extraction of PAEs from soya-bean milk samples.

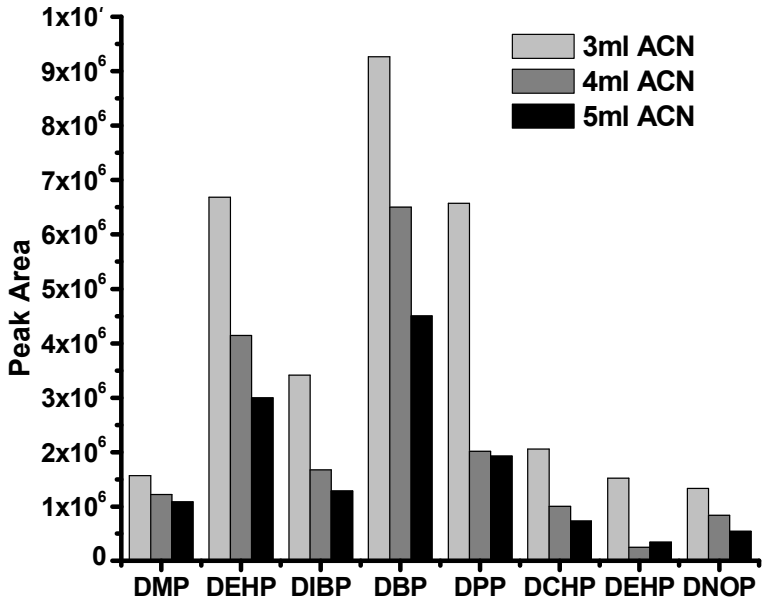

Fig.1 Effect of ACN volume on the extraction efficiencies of PAEs from soybean milk. 5 mL soya-bean milk spiked with PAEs at the concentration of 30 ngg^{-1}. Centrifuge rate, 4000 rpm; centrifuge time, 5 min; volume of ACN in DLLME step, 0.8 mL; extraction solvent, carbon tetrachloride (100 μL); volume of ultrapure water in DLLME step, 5 mL; centrifuge rate in DLLME step, 4000 rpm; and centrifuge time in DLLME step, 5 min, separation system, GC, sample volume, 1 μL.

Optimization of salt concentration

Salt (NaCl) adding may have two effects on the extraction efficiencies of PAEs. One is that the salt addition can increase the amount of PAEs diffused into the extractant solvent to improve the formation of two-phase system; the other is that with salt addition increase the salting-out effect could reduce the solubility of the PAEs in water, and thus enhance the PAEs' concentration in the extract solvent phase. In the experiment, 0.3, 0.4, 0.5, 1.0, 1.5 and 2 g NaCl were added into soybean milk samples which were spiked with the PAEs at concentration of 30 ngg^{-1}, and the highest signal was obtained for 0.5 g NaCl as shown in Fig. 2.

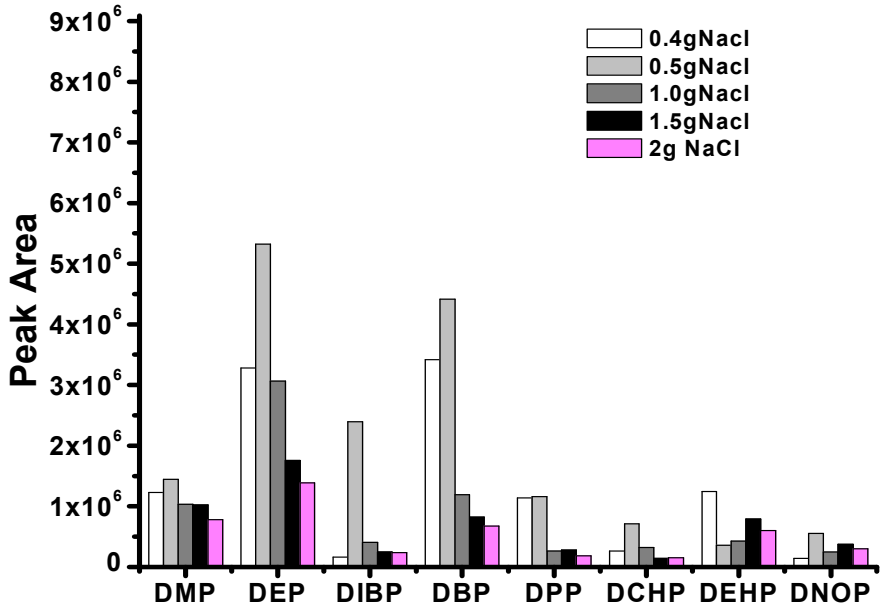

Fig.2 Influence of salt concentration on the peak areas of PAEs. Extraction conditions: 5 mL soybean milk spiked with PAEs at concentration of 30 ngg^{-1}; volume of ACN in the first step, 3 mL; centrifuge rate, 4000 rpm; centrifuge time, 5 min; volume of ACN in the second step, 0.8 mL; extraction solvent, carbon tetrachloride (100 µL); volume of ultrapurewater, 5mL; centrifuge rate, 4000 rpm; and centrifuge time, 5min; separation system, GC; sample volume, 1 µL.

Optimization of parameters in DLLME process

Optimization of ACN volume in DLLME step

To obtain the optimal volume of ACN in DLLME step, various experiments were carried out by using different volumes of ACN in the range of 0.2–1.2 mL with an interval of 0.2 mL (shown in Fig.3). The results showed that the signals of the PAEs were increased initially with the volume of ACN up to 1.0 mL, but decreased thereafter. Therefore, 1.0 mL ACN was selected as the optimal disperser volume.

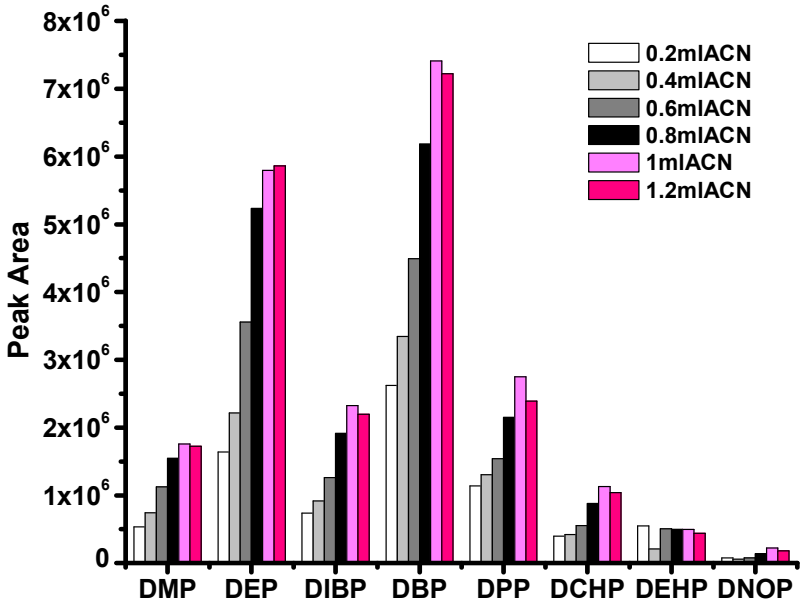

Fig.3 Influence of ACN volume on the extraction efficiency. Experimental conditions: Extraction condition: 5 mL soya-bean milk spiked with PAEs with the concentration of 30 ngg^{-1}. Salt, 0.5 g; volume of ACN in first step, 3 mL; centrifuge rate, 4000 rpm; centrifuge time, 5 min; extraction solvent, carbon tetrachloride (100 µL); volume of ultrapurewater in DLLME step, 5 mL; centrifuge rate in DLLME step, 4000 rpm; and centrifuge time in DLLME step, 5 min; separation system, GC; sample volume, 1 µL.

Selection of extraction solvent in DLLME process

The choice of an appropriate extraction solvent plays a key role for a DLLME process. When selecting an extraction solvent, there are five requirements to consider: (a) higher density than water, (b) good chromatographic behavior, (c) capable for extracting interested compounds, (d) low solubility in water and (e) able to form a two-phase system (cloudy solution) when injected into an aqueous solution in the presence of a dispersive solvent[22, 25, 29]. In order to achieve the optimal extraction efficiency of PAEs from 1 mL ACN, 100 µL carbon tetrachloride, 1,1,1-TCE, tetrachloroethylene and chlorobenzene were added, respectively. The results in Fig.4 revealed that CCl_4 presented the highest peak areas among the four extraction solvents tested. Therefore, CCl_4 was selected as the extraction solvent for this study.

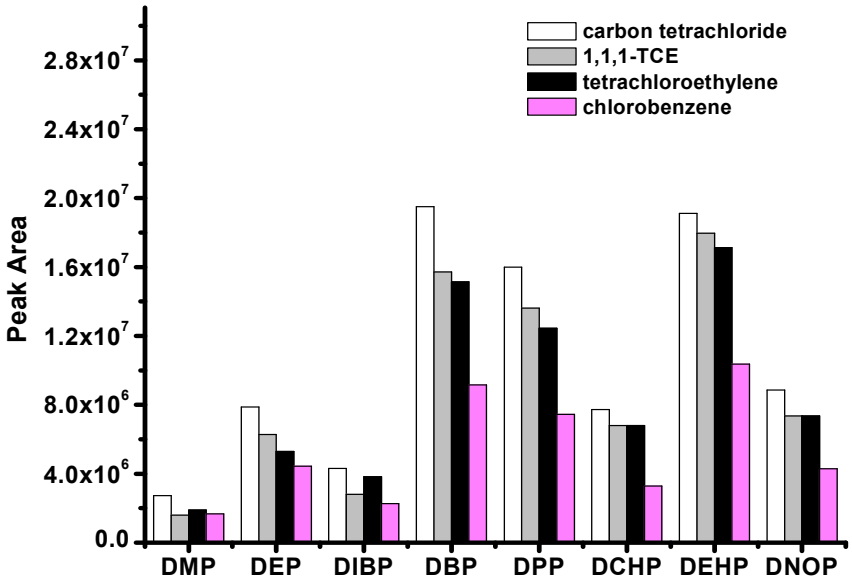

Fig.4 Effect of extraction solvent on the peak areas of PAEs in DLLME from soybean milk. Experimental conditions: volume of ultrapurewater in DLLME step, 5 mL; volume of ACN in DLLME step, 1 mL; centrifuge rate in DLLME step, 4000 rpm; centrifuge time in DLLME step, 5 min; separation system, GC; sample volume, 1 µL.

Optimization of extraction solvent volume in DLLME process

Different volume of CCl_4 in the range of 20–100 µL with an interval of 20 µL was tested in 5 mL ultrapurewater mixed with 1 mL upper organic phase of ACN obtained from the first step. The results in Fig.5 showed that 40 µL of extraction solvent volume produced the highest peak signals, and 40 µL was considered to be the optimal solvent volume for the DLLME process.

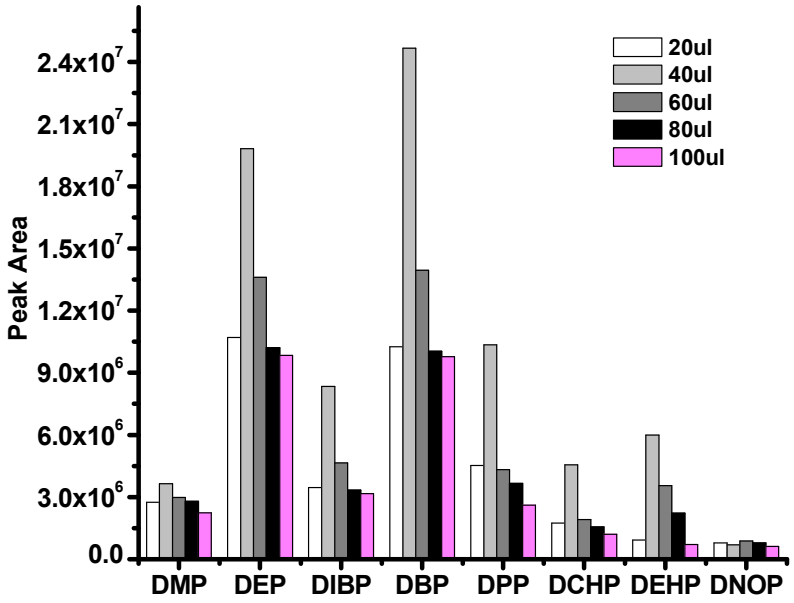

Fig.5 Optimization volume of the extraction solvent. Extraction condition: 5 mL soybean milk spiked with PAEs at concentration of 30 ngg^{-1}. Salt, 0.5 g; volume of ACN in first step, 3 mL; centrifuge rate, 4000 rpm; centrifuge time, 5 min; volume of ACN in DLLME step, 1 mL; volume of ultrapurewater in DLLME step, 5 mL; extraction solvent, variable amount of carbon tetrachloride; centrifuge rate in DLLME step, 4000 rpm; centrifuge time, 5 min. Separation system, GC; sample volume, 1 µL.

Validation of the method and analysis of the real samples

Validation of the method

To evaluate the proposed DLLME-GC-MS method, the linearity, correlation coefficients (r^2), relative standard deviations (RSDs), the limits of detection (LODs), limits of quantification (LOQs) and perconcentration factors (PFs) were determined. The results were summarized in Table 1. LODs and LOQs of the PAEs were found to be in the range of 0.57—0.79 and 1.90—2.63 ngg^{-1}, respectively. The former were determined based on the signal-to-noise ratio (S/N) of 3 and the latter to be 10. Linearities varied in the range of 1—16000 ngg^{-1} with the correlation coefficients of 0.9993–0.9998. The precisions of the method were 2.9 –3.2 in terms of RSD based on triplicate measurements. Furthermore, the preconcentration factors (PFs) were from 200 to 260. For the definition and calculation of PFs, the information could be found in an early report.[23]

Table-1: Evaluation on analytical performance of DLLME and GC/MS determination of the selected PAEs.

Linear equation of analytes		R^2	LOD (ngg^{-1})	LOQ (ngg^{-1})	RSD (%)	PF (fold)
DMP	$Y=6.52x10^5X+2.72x10^3$	0.9994	0.62	2.07	3.2	241
DEP	$Y=8.83x10^5X+1.63\ x10^3$	0.9995	0.57	1.90	3.0	260
DIBP	$Y=5.82x10^5X+4.46\ x10^3$	0.9995	0.63	2.10	2.9	235
DBP	$Y=8.56x10^5X+1.25\ x10^3$	0.9994	0.59	1.97	3.0	246
DCHP	$Y=3.54x10^5X+1.22\ x10^3$	0.9998	0.75	2.50	3.1	221
DEHP	$Y=2.87x10^5X+1.81\ x10^3$	0.9993	0.76	2.53	3.2	212
DPP	$Y=5.37x10^5X+3.43\ x10^2$	0.9995	0.68	2.27	3.0	230
DNOP	$Y=2.76x10^5X+1.11\ x10^3$	0.9996	0.79	2.63	2.9	200

Analysis of the real samples

The proposed method was applied to determine the PAEs in five different brands of soybean milks, which were bought from local markets. The DLLME was employed for the sample pretreatment and the GC-MS was used for the separation and detection of the PAEs in the real samples. The results in Table 2 showed that trace PAEs contaminations were detected in all five samples. A typical GC-MS chromatogram of soybean milk and mass spectra of DCHP with m/z 149 and 163 was showed in Fig.6. To investigate the effect of sample matrix on the accuracy of the determination, the recoveries were measured by spiking three different concentrations of PAEs into the samples. The recoveries were from 79.0 to 110% (Table 3) which demonstrated the feasibility of DLLME-GC-MS for the determination of PAEs in soybean milks.

Table-2:Concentrations of PAEs in different brands of soybean milks (ngg^{-1}).

Milk sample	DMP	DEP	DIBP	DBP	DCHP	DEHP	DDP	DNOP
Brand#1	ND	ND	ND	ND	ND	58.0	ND	ND
Brand#2	ND	ND	ND	2.49	ND	ND	ND	ND
Brand#3	ND	7.53	ND	75.2	ND	16.0	ND	ND
Brand#4	ND	ND	ND	ND	11.0	ND	ND	ND
Brand#5	ND	34.2	ND	ND	3.52	ND	ND	ND

Abbreviation:ND, Not detected.

Table-3： Recovery of PAEs in brand 2# soybean milk samples (n=3).

Analytes	Sample (ngg^{-1})	Spiked amout (ngg^{-1})	Detected amount (ngg^{-1})	Recovery (%)
DMP	ND	3.00	2.69	89.7
		6.00	5.65	94.2
		12.0	11.2	93.3
DEP	ND	3.00	2.54	84.7
		6.00	5.79	96.5
		12.0	11.8	98.3
DIBP	ND	3.00	2.70	90.0
		6.00	5.32	88.7
		12.0	11.4	95.0
DBP	2.49	3.00	5.53	101
		6.00	8.25	96.0
		12.0	15.0	104
DCHP	ND	3.00	2.85	95.0
		6.00	5.43	90.5
		12.0	11.5	95.8
DEHP	ND	3.00	3.29	110
		6.00	5.66	94.3
		12.0	12.2	102
DDP	ND	3.00	2.37	79.0
		6.00	5.82	97.0
		12.0	11.9	99.2
DNOP	ND	3.00	2.66	88.7
		6.00	5.29	88.2
		12.0	12.2	102

Abbreviation: ND, Not detected.

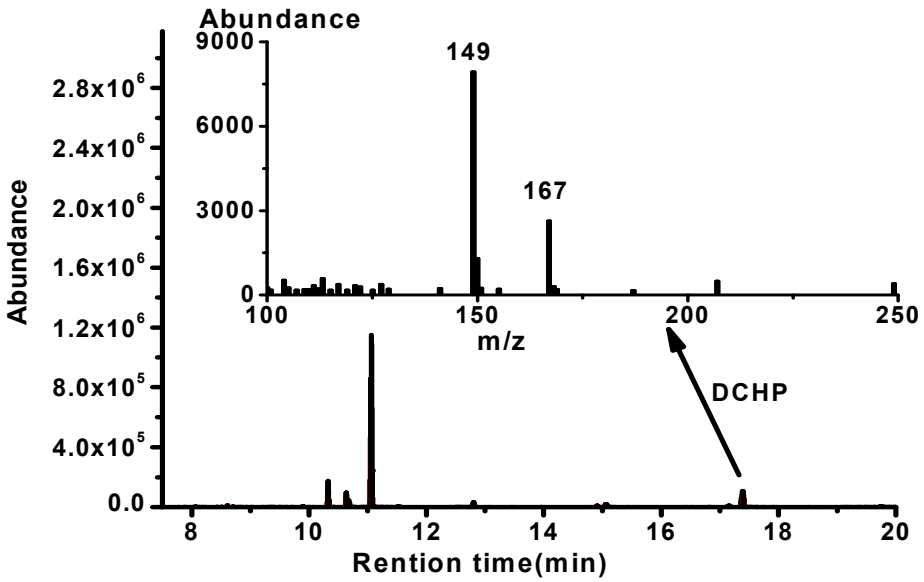

Fig.6 Typical GC-MS chromatogram of brand 4# soybean milk and mass spectra of DCHP, only scans m/z 149 and 163.

Comparison of DLLME with other methods

Table 4 indicates the values of LODs LR, RSD, the extraction time and the sample volumes of the DLLME and other methods for the extraction and determination of PAEs from the similar matrix. From the table, we can see that the present DLLME method offers some advantages of lower LODs, wider linear range, simple extraction procedure, and less-time consuming sample preparation. It is also revealed that the DLLME method was a sensitive, rapid and reproducible technique that could be used for extraction, preconcentration and determination of PAEs in a complex matrix such as soy-bean milk.

Table-4 Comparison of DLLME with other methods for determination of PAEs.

Method	LOD(ngg^{-1})	LR(ngg^{-1})	RSD(%)	Extraction time(min)	Sample volume(mL)	Ref.
SPE-LC-MS/MS[(a)]	0.2-0.6	1-1200	3-5	30	10	30
LLE-LC-MS[(b)]	4-9	20-900	1-2	20	100	31
LLE-LC-MS/MS[(c)]	0.01-0.5	--	2-6	100	3	32
DLLME-GC-MS	0.57-0.79	1-16000	2.9-3.2	15	5	this method

(a) Solid-phase extraction–liquid chromatography–mass spectrometry–mass spectrometry.

(b) Liquid–liquid extraction–liquid chromatography–mass spectrometry.

(c) Liquid–liquid extraction–liquid chromatography–mass spectrometry–mass spectrometry.

Conclusion

In this study, dispersive liquid–liquid microextraction (DLLME) was coupled with GC-MS for the determination of phthalate acid esters (PAEs) in soybean milks. Acetonitrile was first used to extract PAEs from soybean milks and then facilitated to use carbon tetrachloride in DLLME. The sedimented organic phase could be subjected to GC-MS for the separation and the detection. It was observed that all trace PAEs contaminations were present in all the five samples. By using of the DLLME, the preconcentration factors for the PAEs were in the range of 200-260 folds.

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