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A Vortex-Assisted Microextraction Based On Deep Eutectic Solvents for Determination of Four Parabens from Cosmetic Baby Oils and Optimization by Box-Behnken Design

Sezen Sivrikaya Özak

Department of Polymer Engineering, Faculty of Technology, Düzce University, Düzce, TURKEY
Corresponding author: sezensivrikaya@duzce.edu.tr
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ABSTRACT

This study presents microextraction and determination of four parabens by vortex-assisted microextraction based on deep eutectic solvents (DESs) in cosmetic baby oils. The most suitable DES, ChCl-ethylene glycol mole ratios of DES were determined as 1:2 for use in this study. The effect of DES types has been explored at traditional one factor experiment at a time. The effect of DES volume, dilution solvent volume and vortex time on extraction recovery were examined and optimized by the Box-Behnken design. After optimum conditions were determined, vortex-assisted microextraction based on DES, 0.1-100 µg mL^{-1} concentration in the range of the calibration curve was plotted for all parabens. The recovery values of parabens in cosmetic baby oil samples were in the range of 82.02-101.95% and the RSDs were varied from 1.64% to 2.91%. This developed method is very suitable and effective method for the extraction of parabens from cosmetic products of similar structure.

Keywords: Deep eutectic solvents, paraben, liquid phase microextraction, Box-Behnken design

Kozmetik Bebek Yağlarında Dört Parabenin Tayini için Derin Ötektik Çözücülere Dayanan Vorteks Destekli Mikro Ekstraksiyon ve Box-Behnken Tasarımı ile Optimizasyon

ÖZET

Bu çalışma kozmetik bebek yağlarında derin ötektik çözücülere (DES'ler) dayalı vorteks destekli mikroekstraksiyon ile dört parabenin mikro ekstraksiyonu ve tayinini sunmaktadır. En uygun DES, ChCl-etilen glikol mol oranları bu çalışmada kullanılmak üzere 1:2 olarak belirlenmiştir. DES türlerinin etkisi, geleneksel tek faktörlü deneyde araştırılmıştır. DES hacmi, seyreltme çözücü hacmi ve vorteks süresinin ekstraksiyon geri kazanımı üzerindeki etkisi Box-Behnken tasarımı ile incelenmiş ve optimize edilmiştir. Optimum koşullar belirlendikten sonra, DES'e dayalı vorteks destekli mikro ekstraksiyon, kalibrasyon eğrisi 0.1-100 µg mL^{-1} konsantrasyon tüm parabenler için çizildi. Kozmetik bebek yağı numunelerindeki parabenlerin geri kazanım değerleri % 82.02-101.95 aralığındadır ve RSD'ler %1.64 ile %2.91 arasında değişmektedir. Bu geliştirilen yöntem, benzer yapıdaki kozmetik ürünlerden parabenlerin ekstraksiyonu için çok uygun ve etkili bir yöntemdir.

Anahtar Kelimeler: Derin ötektik çözücüler, paraben, sıvı faz mikroekstraksiyon, Box-Behnken tasarımı

I. INTRODUCTION

Parabens are alkyl esters of p-hydroxybenzoic acid, and they are consist of many different alkyl groups such as methylparaben (MP), ethylparaben (EP), isobutylparaben (iBP), butylparaben (BP), isopropylparaben (iPP), propylparaben (PP), and benzylparaben (BeP). As a feature of parabens, parabens having an excess of alkyl chain length have high antimicrobial and antibacterial properties and low solubility in water [1-4]. Parabens are extensively used in baby products because they are cheap and very effective preservatives. However, preservatives can stop the growth of molds and bacteria that can disrupt the contents of a product, such as baby skin lotion or they can harm the baby. In newborns, parabens are less likely to cause an allergic reaction than other commercial preservatives. If in the human body, parabens act as estrogen hormones in women. There are many concerns that this may affect human health [5, 6].

In addition to their antibacterial activities, parabens exert an estrogenic effect that can change the endocrine system in a beneficial or harmful way. It has also been found that parabens induce in vitro proliferation of breast cancer cells. Despite the small number of studies with people, that is associated with adverse health consequences of exposure to parabens is too much evidence. Therefore, maternal urinary paraben levels have been associated with negative outcome of pregnancies, decreased neonatal thyroid hormones and allergic disorders. Childhood exposure to methylparaben and propylparaben has been associated with timing of puberty [3]. In recent years, a large number of paraben-free cosmetics have been marketed due to the increasing interest of consumers in healthy products. However, due to the increasing demand, cosmetic companies make "paraben free" label fraud in cosmetic samples [7]. For these reasons, it is of great importance to develop an accurate and reliable method for determining parabens in cosmetic products. It is very important to make the correct determination of parabens.

The content of some cosmetic products have some negative effects on people. To prevent the use of uncontrolled cosmetic products, before the products are placed on the market, it must be thought that these products are true for human health [1]. Due to the complex nature of the sample in cosmetic products, pretreatment of samples is a very important step. For extraction of parabens are there many different methods, such as liquid phase microextraction, dispersive liquid-liquid microextraction (DLLME), solid phase micro-extraction (SPME), molecularly printed polymers extraction, stir bar absorbent extraction, solidified floating vesicular coacervative drop microextraction, and supercritical fluid extraction from different matrixes [8-14].

The microextraction techniques have been an effective method in preparing the sample because of its important advantages such as the low amount of waste, presence of a small amount of organic solvent, simplicity, speed and high enrichment coefficient, in recent years [15, 16]. A variety of analytical methods are used for the extraction and determination of parabens, including high performance liquid chromatography (HPLC) with different detector, gas chromatography (GC), capillary electrophoresis (CE), ultra-HPLC, HPLC/MS-MS, liquid chromatography-mass spectrometer (LC-MS/MS), and some other techniques [17-23]. In this study, HPLC with an ultraviolet detector (UV) was used to rapidly to analyze the extracted parabens.

Owing to the many superior chemical and physical properties of DESs, it has been drawing attention in lately. DESs are achieved by both hydrogen bond acceptors and hydrogen bond donors by intermolecular hydrogen bond coupling according to a particular stoichiometry [24, 25]. DESs are the solvents that biodegradable, easy to prepare, non-toxic, and so they are widely used in electrochemistry, chemical separation, organic synthesis studies. They are accepted as a new family of ionic liquids (IL) so they show parallel physical properties. However, DESs have some superior properties compared to ILs, such as environmentally friendly, high purity, easy preparation, low cost, and biodegradability [26, 27]. To develop vortex-assisted microextraction based on DES for determination and extraction of parabens in cosmetic baby oils is the purpose of study. Thus, some products that should not be used for the protection of baby skin and health have been identified. This method consists of two steps. In the first step, the DESs were synthesized by ChCl and ethylene

glycol. In the second step, the DES was used as a solvent in the vortex assisted microextraction method for microextraction and determination of four parabens by HPLC-UV in cosmetic baby oils. One factor, types of DES, was studied with one factor experiment at a time. In this study, 3 other components such as vortex time, DES volume, dilution solvent volume were examined by Box-Behnken design (BBD) in this study. After determining the optimum conditions, for the accuracy of this developed method was used real samples.

II. EXPERIMENTAL

A. APPARATUS

The samples were analyzed by an Agilent Technologies 1200 Series HPLC with an auto sampler, a quaternary pump, a degasser, a column oven, and a VWD-detector (Agilent, USA). An ACE-C18 column (4.6 i.d. x 250 mm, 5 μm, Mac-Mod, Chadds Ford, PA, USA) was used for chromatographic separation. A vortex mixer (VWR international model, Germany), a NF 200 centrifuge (Nüve, Ankara, Turkey) and a thermostat hotplate mixer (IKA C-MAG HS-7, Staufen, Germany) was utilized in the preparation of samples and extraction steps. A Fourier transform-infrared spectrometer Frontier Optica (PerkinElmer, Shelton, CT, USA) was operated to identify the functional groups of ethylene glycol, choline chloride and DES with the KBr pellet technique.

The mobile phase was used by creating a mixture of acetonitrile and water with a 35-minute program. Flow rate, column temperature, injection volume were set to be 1 mL min^{-1}, 20 μL, and 30°C, respectively. The parabens were stated by adjusting the wavelength of HPLC to 254 nm.

B. CHEMICALS AND REAGENTS

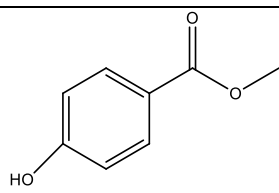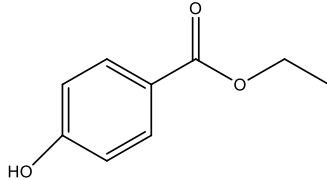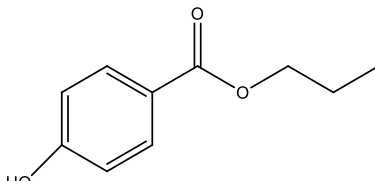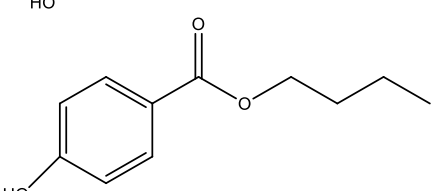Choline chloride ($C_5H_{14}ClNO$) (ChCl) (98%), ethylene glycol ($C_2H_6O_2$) (>99%), acetic acid (CH_3COOH) (99%), glycerol ($C_3H_8O_3$) (99%), urea (CH_4N_2O) (99%), HPLC grade acetonitrile (C_2H_3N) and standards of methylparaben ($C_8H_8O_3$), ethylparaben ($C_9H_{10}O_3$), propylparaben ($C_{10}H_{12}O_3$) and butylparaben ($C_{11}H_{14}O_3$) (>98.5%) were supplied from Sigma Aldrich (Steinheim, Germany). The molecular structure and properties of these parabens used in this study are given in Table 1. Distilled water was prepared with a Milli-Q system (Millipore, Billerica, MA, USA).

The stock solution with four parabens was formed in acetonitrile at a concentration of 1000 μg mL-1 and these solutions were hidden at 4 ° C. The solutions used in the tests were designed by diluting the stock solution with acetonitrile to be used at certain concentrations. These prepared solutions were given into the HPLC-UV system and extraction recoveries were calculated from the peak areas. The cosmetic baby oil samples were supplied from different cosmetic markets in Turkey. Paraben-free baby oil was used for validation and optimization studies and the first analysis was performed with this product. Paraben standards were added to some cosmetic baby oil samples at different concentrations, spike/recovery studies were performed, and then the microextraction procedure was followed.

C. PREPARATION OF DESs

Eight different types of DESs were prepared by using ChCl-urea, ChCl-acetic acid, ChCl-ethylene glycol, and ChCl-glycerol at different molar ratios in the present study. The mixtures were stirred until clear, colorless liquids formed with magnetic stirrer at 80–100°C. The prepared DESs and mole ratios are listed in Table 2 in this study.

*Table 1. The properties and molecular structure of parabens in this study*

Compound Name	Structure	Molecular weight (g mol^{-1})	Formula
Methylparaben		152.15	$C_8H_8O_3$
Ethylparaben		166.18	$C_9H_{10}O_3$
Propylparaben		180.20	$C_{10}H_{12}O_3$
Butylparaben		194.22	$C_{11}H_{14}O_3$

Table 2. Prepared DESs and mole ratios

DES	Hydrogen bond acceptor (HBA)	Hydrogen bond donor (HBD)	HBA/HBD (mol/mol)
DES1	ChCl	Urea	1:1
DES2	ChCl	Urea	1:2
DES3	ChCl	Acetic acid	1:1
DES4	ChCl	Acetic acid	1:2
DES5	ChCl	Glycerol	1:1
DES6	ChCl	Glycerol	1:2
DES7	ChCl	Ethylene glycol	1:1
DES8	ChCl	Ethylene glycol	1:2

D. VORTEX-ASSISTED MICROEXTRACTION PROCEDURE BASED ON DES

Vortex-assisted microextraction procedure based on DES was used as previous method [28]. 0A 0.5 g cosmetic baby oil sample was flowed into a tube with 15 mL volume. Next, 200 μL of DES was appended to the solution. Then, the resulting solution was mixed with a vortex for 3 minutes. After 5 minutes of centrifugation at a constant speed of 4000 rpm, two phases were observed to be separated. Finally, the DES phase containing the parabens was removed from the tube by the aid of a micropipette and given into the HPLC-UV and concentration of parabens were determined. A schematic representation of the vortex-assisted microextraction procedure based on DES is given in Figure 1.
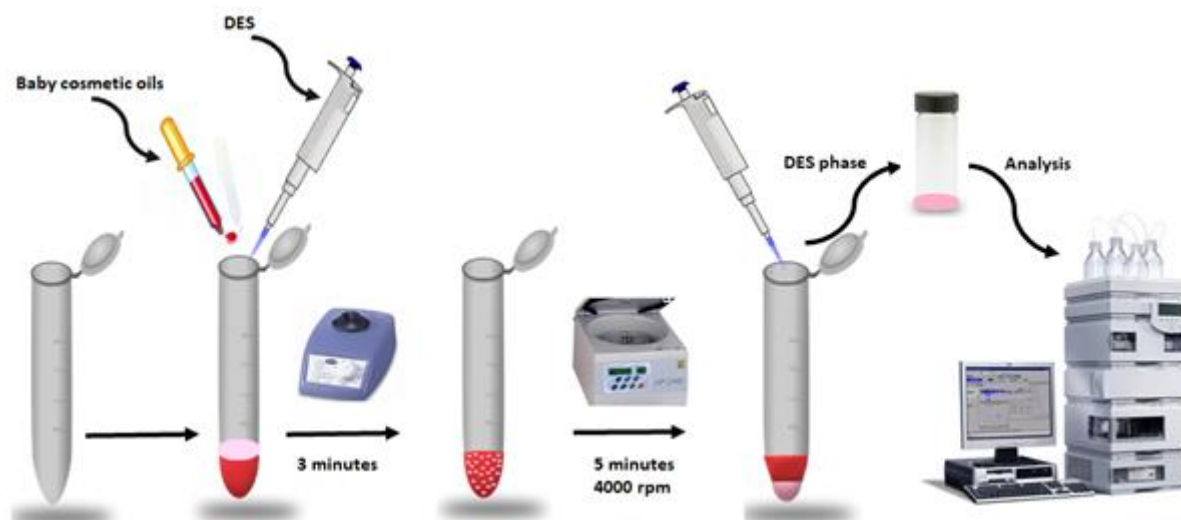
Figure 1. Vortex-assisted microextraction based on DES procedure

E. OPTIMIZATION STUDIES

4 factors such as DES volume, DES type, vortex time and dilution solvent volume were selected to study the extraction efficiency in this study. DES types from these parameters were studied with one factor experiment at a time. Box-Behnken Design was applied to provide the most suitable conditions for other parameters. Data and design analysis of Box-Behnken design were applied using Design-Expert 12.0 software.

III. RESULTS AND DISCUSSION

A. FTIR STUDIES

FTIR spectra are given in the previous study. FTIR spectra were examined in order to show the structure of choline chloride, ethylene glycol and DES8 and the results obtained are presented in Figure 2. When the FTIR spectrum of choline chloride and ethylene glycol was investigated, peaks at 3391 cm^{-1} and 3374 cm^{-1}, indicate the presence of O-H vibration peaks, respectively. When the FTIR spectrum of choline chloride is examined, the peak at 1086 cm^{-1} is due to the presence of C-N vibration. DES8 appears to shift the OH vibration of 3402 cm^{-1}. Changes in the FTIR spectra of choline chloride and ethylene glycol are indicative of hydrogen bonds when DES is formed [29].

B. EFFECT OF THE COMPOSITION OF THE DES

The DES composition is of great importance in extraction studies because it is the most effective parameter for separating and determining analytes from the sample. Therefore 8 DES with different DES composition were prepared. Since the viscosities of DES1 and DES7 were very dense, they could not be used in this study. Microextraction of the parabens was performed with the remaining 6 different DESs and Figure 3 shows that DES8 has higher extraction efficiency than other DESs. Therefore, for the rest of the study, DES8 (ChCl-ethylene glycol) was used as the most suitable DES.
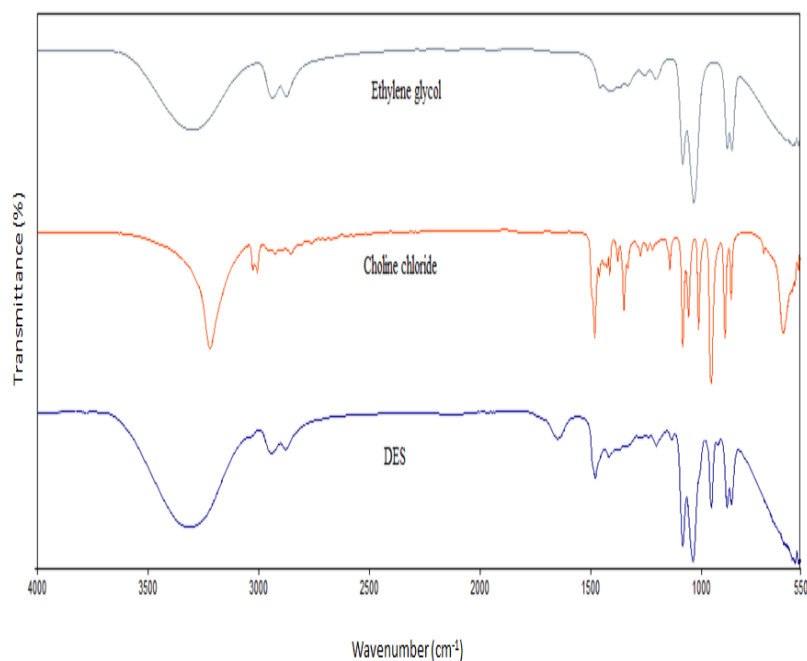
Figure 2. *FTIR spectra of ChCl, ethylene glycol and DES8*
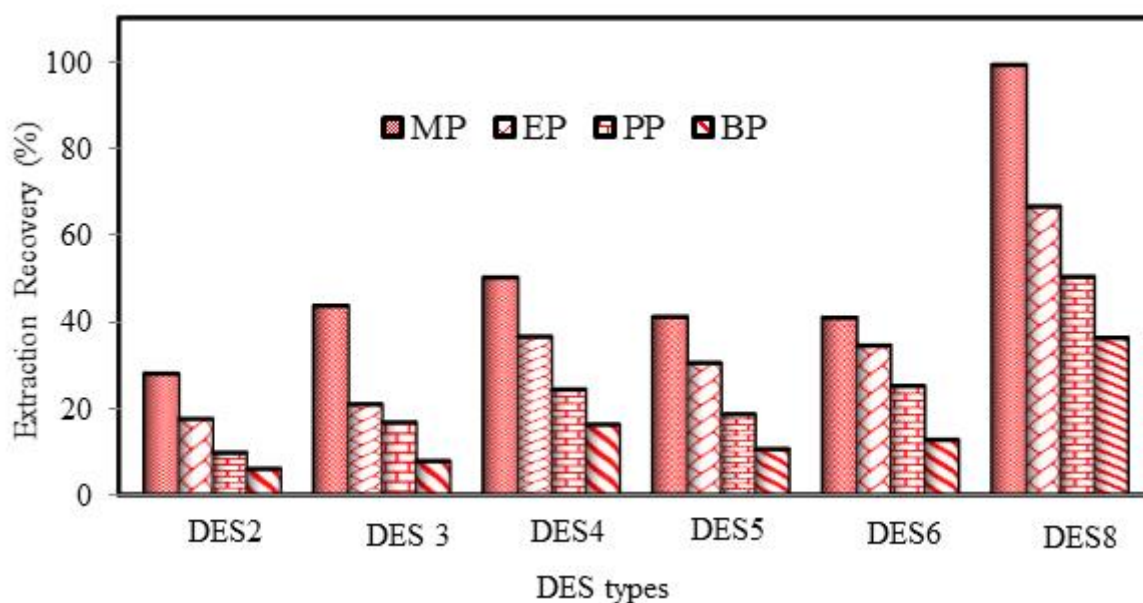
Figure 3. *Effect of DESs types on the extraction recoveries of parabens*

C. OPTIMIZATION OF THE EXTRACTION CONDITION

After determining the best DES composition, vortex time, DES volume, and dilution solvent volume were determined by Box-Behnken Design [30-32]. For this purpose, BBD was carried out with three different factors and three levels in order to obtain maximum extraction efficiency. Investigated data for BBD are given in Table 3.

Table 3. The factors and levels of the Box-Behnken design

Variable	Key	Level	
		Low	High
DES volume (µL)	A	100	500
Dilution solvent volume (mL)	B	0	2
Vortex time (min.)	C	0	10

Optimum experimental conditions were determined by evaluating three variables and their interactions. According to Box-Behnken data analysis results, a quadratic equation was obtained. It is expressed as follows:

$$R= 87.20 + 16.04*A - 2.98*B + 7.83*C - 0.7930*AB + 3.79*AC - 6.00*BC - 26.63A^2 - 5.14B^2 - 8.54C^2$$

The experimental design consists of 12 tests and 3 central points and was done with Design-Expert 12.0. Methyl paraben was chosen for random optimization due to changes in the recovery of the four parabens. From the data obtained, it is seen that the determination coefficient (R2) is 96.97%, which showed that the model fits well with the variations. In order to see the fit between the model and the actual system, the important parameters obtained by analysis of variance (ANOVA) are shown in Table 4. When the table is examined, the model F-value of 17.78 and p values less than 0.0500 prove that model terms are significant. Box-Behnken data analysis results show that A and C are important model terms. B value means that it is not significant because it has a value higher than 0.1. This shows that dilution solvent volume is not effective in this developed method.

Table 4. Analysis of variance of the predicted model of paraben obtained with ANOVA

Source	Sum of Squares	Degree of freedom	Mean Square	F-value	p-value
Model	5625.45	9	625.05	17.78	0.0028
A	2058.77	1	2058.77	58.56	0.0006
B	70.86	1	70.86	2.02	0.2149
C	490.67	1	490.67	13.96	0.0135
AB	2.52	1	2.52	0.0715	0.7998
AC	57.44	1	57.44	1.63	0.2573
BC	144.06	1	144.06	4.10	0.0988
R^2	0.9697				

The 3D response surfaces plots obtained from AB, BC and AC interaction effect are demonstrated in Figure 4. The DES volume, which is an important parameter for extraction recovery, ranges from 100 to 500 µL. However, it is seen from Figure 4(a) and Figure 4(b) that the extraction recovery increases from 100 µL to 300 µL and then decreases after 300 µL. For this reason, the most appropriate DES volume to be used in the study was determined as 300 µL. Another parameter effective on extraction recovery is vortex time. The vortex time ranges from 0 to 10 minutes, and when the examined in Figure 4(b) and Figure 4(c), it can be seen that the vortex time increases up to 5 minutes and there is no significant change afterwards. Therefore, in this study, 5 minutes of vortex time was determined as the optimum value. The dilution solvent volume ranges from 0 to 2 mL. The dilution solvent volume was not significant according to the p test result. It is seen from Figure 4(a) and Figure 4(c), that there is no need to use dilution solvent volume in this study.
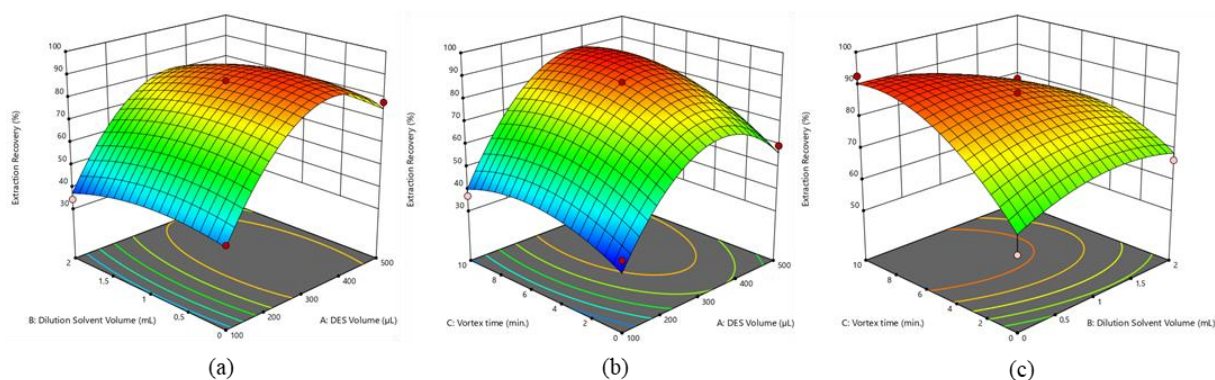
Figure. 4. *Response surface for methylparaben using the Box-Behnken design obtained by plotting* ***(a)*** *DES volume versus dilution solvent volume,* ***(b)*** *DES volume versus vortex time and* ***(c)*** *dilution solvent volume versus vortex time.*

D. VALIDATION OF THIS METHOD

Under optimum conditions, linear calibration curves for four parabens were generated in the concentration range of 0.1 to 200 µg mL^{-1}. The calibration curves of the parabens showed good linearity (R^2>0.9992) over wide concentration ranges. The limit of detection (LOD) values were calculated as 3s/m and the limit of quantification (LOQ) were calculated as 10s/m, where s represents the standard deviation of the eleven blank solutions and m represents the slope of the calibration curves. All analytical performance values are demonstrated in Table 5. It was determined that the relative standard deviation (RSD, %) values were in the range of 1.64-2.91% for analysis of nine analysis of 2.5 µg mL^{-1} of methylparaben, ethylparaben, propylparaben and butylparaben.

Table 5. *Results of method validation*

Analyte	Linearity (µg mL^{-1})	Regression Equation	Correlation coefficient (R^2)	LOD (µg mL^{-1})	LOQ (µg mL^{-1})	RSD (%) (2.5 µg mL^{-1})
Methylparaben		A = 208.25C+25.69	0.9994	0.053	0.177	2.38
Ethylparaben	0.1-100	A = 148.76C+106.35	0.9992	0.061	0.205	1.64
Propylparaben		A = 98.66C+50.76	0.9995	0.049	0.163	2.91
Butylparaben		A = 56.8C+60.64	0.9992	0.052	0.174	2.16

E. APPLICATION OF THE DEVELOPED METHOD TO COSMETIC BABY OILS

The different brand baby oil products were obtained from vendors in the market. Within the framework of the proposed method, two different concentrations were added to the cosmetic baby oils purchased from the markets, thus the precision of the method was demonstrated. When the Table 6 was examined, it was found that this advanced method was successful for the extraction and determination of parabens in cosmetic baby oil samples, since the recovery values obtained were acceptable and reliable.

Table 6. *Application of the developed method to different brand cosmetic baby oils (N=3)*

Parabens	Spiked level ($\mu g\ mL^{-1}$)	Brand 1		Brand 2		Brand 3		Brand 4	
		Found ($\mu g\ mL^{-1}$)	% R	Found ($\mu g\ mL^{-1}$)	% R	Found ($\mu g\ mL^{-1}$)	% R	Found ($\mu g\ mL^{-1}$)	% R
MP	0	4.99	-	4.40	-	24.29	-	0.55	-
	5	10.18	101.95	8.92	94.95	28.45	97.13	4.81	86.69
	50	53.62	97.51	51.43	94.54	65.26	87.84	44.98	88.98
EP	0	81.99	-	27.07	-	0.21	-	0.49	-
	5	84.67	97.32	31.17	97.17	5.17	99.19	4.67	84.97
	50	120.75	91.48	74.92	97.20	47.38	94.36	41.41	82.02
PP	0	-	-	-	-	-	-	0.30	-
	5	4.70	94.08	4.84	96.73	5.04	100.86	4.88	92.03
	50	47.13	94.25	47.50	95.01	48.67	97.34	42.75	84.99
BP	0	-	-	3.48	-	0.76	-	1.58	-
	5	4.88	97.54	8.44	99.50	5.57	96.61	5.59	88.69
	50	47.72	95.44	52.11	97.43	45.37	89.38	45.38	87.99

IV. CONCLUSION

A novel vortex-assisted microextraction based on deep eutectic solvents method was developed for the determination of parabens of cosmetic baby oil samples. The effects of variable parameters on extraction recovery of parabens were determined and optimized with a Box-Behnken design. After determining the optimum conditions, the method was found to have good linearity, low LODs, and sensitivity. Furthermore, the presence of DES in this method indicates that the method is more environmentally friendly than using the conventional organic solvent. Other advantages of the procedure are that it is a very simple and fast technique, and no organic solvent such as hexane is used. The recovery values of parabens are quite satisfactory as a result of the spike process of different brands of cosmetic baby oils. In view of the results applied to real samples, it shows that when combined with DES8 (ChCl/EG 1:2) vortex assisted liquid-liquid microextraction; parabens were quantitatively separated from cosmetic baby oils. The developed method could be easily used in other cosmetic oil samples.

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