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A green microfluidic method based liquid phase microextraction for the determination of parabens in human urine samples

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ABSTRACT

Development of green approaches have emerged as a challenge that highlight the pressing need for non-toxic solvents, miniaturized method and bio-degradable materials. In this regard, an environmentally-friendly microfluidic system based on natural deep eutectic solvents (DESs) immobilized in agarose membranes was developed to extract parabens from urine samples for the first time. A comprehensive study of the support liquid membrane showed that only 3 µL of camphor and thymol (2:1 molar ratio) was an interesting option as a substitute for conventional (toxic) solvents used to date. Other experimental conditions were optimized and pH 4 (HCl) and 12 (NaOH) were selected as sample and acceptor solution, respectively. Both solutions (sample and acceptor) were fixed at 1 µL min^{-1} as flow rate. The proposed green microfluidic device was successfully applied for the determination of parabens in urine samples with relative recoveries between 86 and 100% for all analytes. Detection limits and quantitation limits were between 0.011–0.093 and 0.31–0.38 µg mL^{-1}, respectively. Relative standard deviation was below 7% for all analytes. Furthermore, the environmentally-friendly solvent (Ca:Ty 2:1) used as SLM offered the same advantages in terms of membrane stability allowing consecutive extractions. Results were compared with experiments previously conducted using conventional (polypropylene) membranes, observing that highly green microextraction systems based on natural and biodegradable materials have proven to be an attractive alternative in microfluidic systems.

1. Introduction

The emergence of down-scaled extraction methods has attracted a great deal of attention over the past two decades. Liquid phase microextraction (LPME) have paved the way to introduce the different sample preparation methods such as single drop microextraction (SDME), hollow-fiber LPME [1,2], among others. Indeed, liquid phase microextraction has been developed towards an easy automatization, enhance sample throughput and improve accuracy and precision [3–5]. Nevertheless, improving miniaturized, green and eco-friendly LPME procedures have still remained a challenging task. In the case of miniaturization, microfluidic methods based LPME have been used as a strategy not only due to comprising small amounts of organic solvents but also because of capability of accelerating mass transfer [6–10], decrease the extraction time, decrease the amount of sample and reagents, and allow consecutive extractions. LPME extractions mostly use polypropylene membranes and have been shown to offer good results in both non-miniaturized [2,4] and miniaturized [9,10] systems. Furthermore, fundamental SLM studies have focused on chemical solvents with some degree of toxicity. Although the reduction of excessive amounts of organic solvents in microfluidic systems is a task that scientists have been very successful, searching for new solvents that can possess eco-friendly advantages is a main issue in these systems. The necessity to replace toxic and volatile by safer solvents has led to apply deep eutectic solvents (DESs) for extraction of different compounds. DESs are expected to replace volatile and toxic conventional as an alternative. DES have been employed for the different extraction techniques for extraction polycyclic aromatic hydrocarbons [11], phenolic compunds [12], organic and inorganic analytes [13,14], etc. To date, our group has previously investigated the possibility of success after using DESs as a supported liquid membrane (SLM) both in traditional systems and in miniaturized systems, offering results with high extraction efficiency [8]. On the other hand, the

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use of homemade gel membranes has turned out to be a great alternative to conventional polypropylene membranes [15–18]. Among the natural biopolymers, agarose has been used, as a green material, in the form of gel flat membrane for liquid based microextraction methods thanks to its inertness, biodegradability and eco-friendliness are of its unique advantages [19]. However, there are not many studies in which biodegradable membranes are used simultaneously with DES and it may influence the extraction efficiency [8]. It seems that coupling the merits of miniaturized procedure based on microfluidic devices, green solvents with eco-friendly advantages and biodegradable materials would be a great advance in sample treatment. The combination of agarose membranes together with the use of non-toxic solvents such as SLM provide great versatility for the extraction of analytes of different nature. In this way, it is intended to optimize the type and the different possible combinations of DES to achieve a green application to the determination of parabens. In this work, we proposed for the first time, a new and fully green microfluidic method for the determination of parabens in human urine samples in order to fulfill all green chemistry requirements. Parabens have been selected due to the growing interest in recent years in analyzing these compounds that are widely used in protective additives in cosmetics, care products and pharmaceuticals and that end up accumulating in the body [20,21]. A comprehensive study was also carried out to develop an efficient ecological supported liquid membrane compatible with biomaterials as solid support as well as the influence of the geometry in the mass transfer.

2. Experimental

2.1. Chemicals and materials

All reagents and chemicals were of analytical grade. Agarose (gelling temperature for 1.5%: 34.5–37.5 °C) was purchased from Merk. Ethyl 4-hydroxybenzoate (EtP), propyl 4-hydroxybenzoate (PrP), butyl 4-hydroxybenzoate (BuP), formic acid, sodium hydroxide and hydrochloric acid were purchased from Fluka-Sigma-Aldrich, Spain. Methanol, 2-nitrophenyl octyl ether (NPOE), dihexyl ether (DHE), and 1-octanol were supplied from Merck (Darmstadt, Germany). Camphor (Ca), DL-menthol (Me), coumarin (Co), and thymol (Ty) were supplied from Sigma-Aldrich (Madrid, Spain). Each stock solution was prepared in methanol (100 mg L^{-1}) and stored at 4 °C in a refrigerator. Working solutions were daily prepared by dilution of the stock solutions with deionized (DI) water. Ultrapure water was obtained using a Milli-Q Plus water purification system (Millipore, Billerica, MA, USA).

2.2. Chromatographic conditions

Separation was carried out using an Agilent 1100 series liquid chromatography (Barcelona, Spain) which was equipped with a G1312A bipump systems, an autosampler G1313A and UV/Vis diode array detector (DAD). Chromatographic separation was performed using a LiChroCART 75–4 Purosphere STAR RP-18e 3 µm (75 mm x 4.0 mm i.d.) (VWR, Spain) proceeded by a guard column Kromasil1 100 Å, C18, 5 µm (20 mm x 4.6 mm i.d.) (Scharlab S.L., Barcelona, Spain). 0.1% formic acid (pH 2.6) and methanol were set as mobile phase A and B, respectively. The flow rate was set at 0.5 mL min^{-1}. The mobile phase was constant at 35% A for two minutes and then a gradient from 35% to 20% A for 6 min was applied, followed by 3 min equilibration time. The injection volume was 7 µL and the wavelength used for DAD was 254 nm for all analytes. The separation was completed in 8 min, with retention times of 3.4, 4.8 and 7.3 min for EtP, PrP and BuP, respectively.

2.3. Preparation of deep eutectic solvent and gel membrane

Based on our previous study, the DESs was synthesized by dissolving a proper amount of HBD and HBA in each other and in an oven at 80 °C for 15 min [8]. The obtained clear liquids were cooled down to room temperature and used as solvent liquid membrane.

The agarose gel membrane was prepared by weighting 0.40 g agarose and added to 100 mL DI water. The solution was then shacked and boiled at 100 °C for 30 min. A Petri dish was filled with the warm solution and kept at room temperature for at least 30 min. Then, it was dried in the oven at 50 °C for 24 h, obtaining a membrane of 5.41 µm thickness. Fig. 1 shows an image of the top (a) and the cross-section (b) by using Scanning Electron Microscope. The formed gel membrane was cut into 30 × 0.5 mm pieces for further use.

2.4. Chip design and liquid phase microextraction operations

A laser ablation cutter (Epilog Mini 24–30 W) was used for fabricating the poly(methyl methacrylate) (PMMA) microfluidic device. Fig. 2 shows a scheme of the proposed microfluidic device. Fabrication conditions were: writing speed of 40%, power of 24%, a resolution of 1500, and a frequency of 5000. The device consisted of two symmetric plates (14 mm length, 70 µm deep and 3 mm wide) containing one channel each (14 mm length, 70 µm deep and 3 mm wide). Six holes of 3 mm were created on each plate for assembling. The agarose membrane was placed between both channels to separate the sample and acceptor phase, and it was impregnated with 3 µL of Ca:Ty (2:1) as supported liquid membrane. The reusable device was closed using six screws. Two holes were drilled for inlet solution and outlet solution in each channel and the sample and acceptor solution were submitted to the device using two micro-syringe pump (Cetoni GmbH, Korbussen, Germany), operating at 1 µL min^{-1}. After 5 min for SLM stabilization (bubble free), the acceptor was collected during 10 min in a micro insert tube and then injected into the HPLC-UV system for analysis.

2.5. Calculations of extraction efficiency

Extraction efficiency was calculated according to the following equation:

$$EE\ (\%) = \frac{n_a}{n_d} x100\% = \frac{V_a\, C_a final}{V_d C_d initial} x100\% \quad (1)$$

Here $n_d\ initial$ was the initial amount of analyte present in the sample and $n_a\ final$ was the final amount of analyte in acceptor solution. V_d was the sample volume and V_a was the acceptor volume. Finally, $C_a\ final$ and $C_d\ initial$ were the initial and final concentration of analyte in the acceptor and sample, respectively.

2.5. Real samples

Urine samples were collected from three different adult female volunteers (prior consent) and each urine sample was spiked at different concentration levels with all compounds and within their calibration range. The samples were adjusted to the optimum pH (4) with an HCl solution before submitting to the microfluidic device.

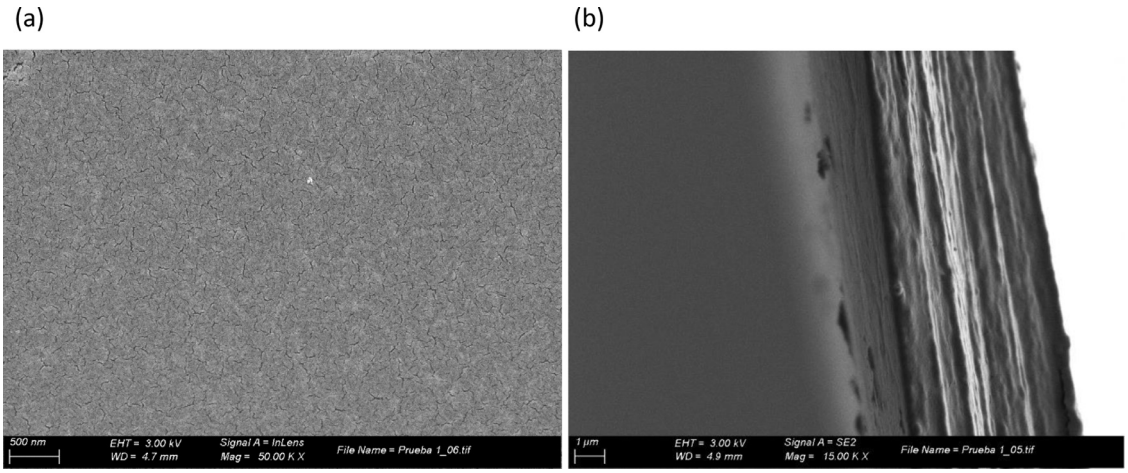

Fig. 1. Image of the membrane using SEM of the (a) cross section and (b) top.

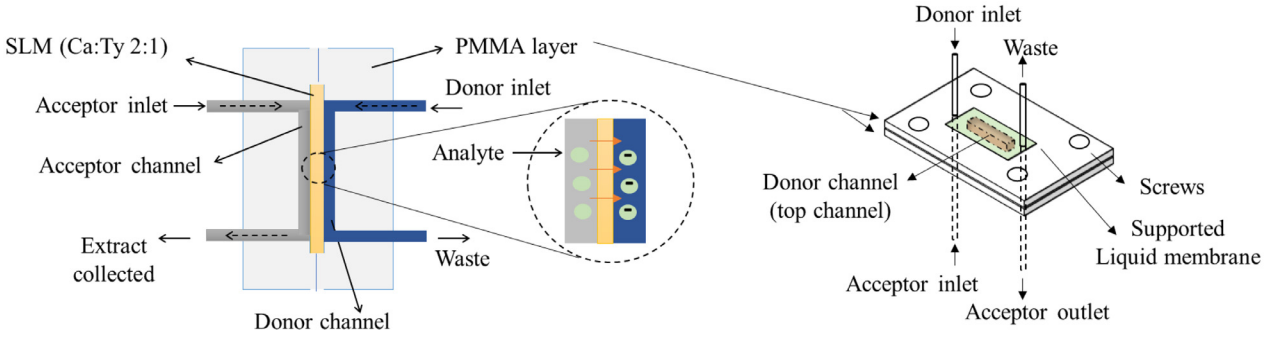

Fig. 2. Scheme of the microfluidic device.

3. Results and discussion

3.1. Supported liquid membrane and agarose membrane composition and

A comprehensive studied was carried out to obtain a complete environmentally green membrane by using natural and ecological solvents as supported liquid membranes and a biodegradable material as membrane support for the determination of parabens by using a microfluidic system based liquid phase microextraction. This study was also compared with non-biodegradable membranes (polypropylene). Based on our previous paraben work [22], preliminary conditions prior optimization were selected at pH 3.5 and pH 12 as sample and acceptor solution, respectively, and 1 µL min^{-1} as flow rates for both solutions. Parabens must be in their neutral form (pH<pKa) in the donor phase and in their ionized form (pH>pKa) in the acceptor phase to ensure the extraction through the membrane under LPME conditions.

Based on our pervious study [8], 0.4% of agarose was selected for preliminary experiments and the study of the supported liquid membrane. DESs should provide some requirements as SLM in microfluidic-based LPME, such as, water immiscibility, non-volatility, affinity towards analytes, and compatibility with PMMA plates. Additionally, their melting point should be well below room temperature and their viscosity should be low for acceleration of passive diffusion and mass transfer. In this study, four non-ionic components were selected to form hydrophobic DESs at room temperature. Camphor and coumarin were selected as HBA components while DL-menthol and thymol were selected as HBD components. Different molar ratio of each solvent was prepared (molar ratios of 2:1, 1:1, and 1:2 of HBA:HBD) to adjust a mixture of HBA and HBD. Additionally, in order to evaluate gel membrane with previous PP membranes, different common synthetic solvents 2-nitrophenyl octyl ether (NPOE), dihexyl ether (DHE) and octanol were investigated as extraction phases in combination with agarose support membranes. Table 1 shows the results obtained for all solvents applied to gel membranes. As seen, the highest extraction efficiency for all analytes was obtained using Ca:Ty (2:1) as extraction phase. No significant differences were observed when the proportion of Ty was increased, only P1 decreased the efficiency by 8%. For this reason, Ca:Ty (2:1) was selected for the study of the agarose concentration. The following experiments were carried out to prepare and test support membranes at

Table 1
Extraction efficiencies (RSD%) of the analytes using different organic solvents as SLM on gel agarose flat membranes.

	Extraction efficiency% (RSD%, $n = 4$)		
	EtP	PrP	BuP
Octanol	16 (3)	24 (4)	24 (6)
DHE	23 (4)	25 (5)	24 (3)
NPOE	25 (4)	27 (4)	24 (5)
SLM (Ca:Ty 1:1)	22 (5)	40 (4)	51 (6)
SLM (Ca:Ty 1:2)	34 (6)	53 (5)	52 (6)
SLM (Ca:Ty 2:1)	40 (5)	57 (6)	51 (4)
SLM (Co:Ty 1:1)	9 (5)	39 (4)	44 (5)
SLM (Co:Ty 2:1)	7 (3)	18 (6)	19 (5)
SLM (Co:Ty 1:2)	6 (3)	12 (4)	14 (4)
SLM (Ca:Me 1:1)	27 (5)	32 (6)	31 (6)
SLM (Ca:Me 1:2)	35 (3)	43 (5)	35 (4)

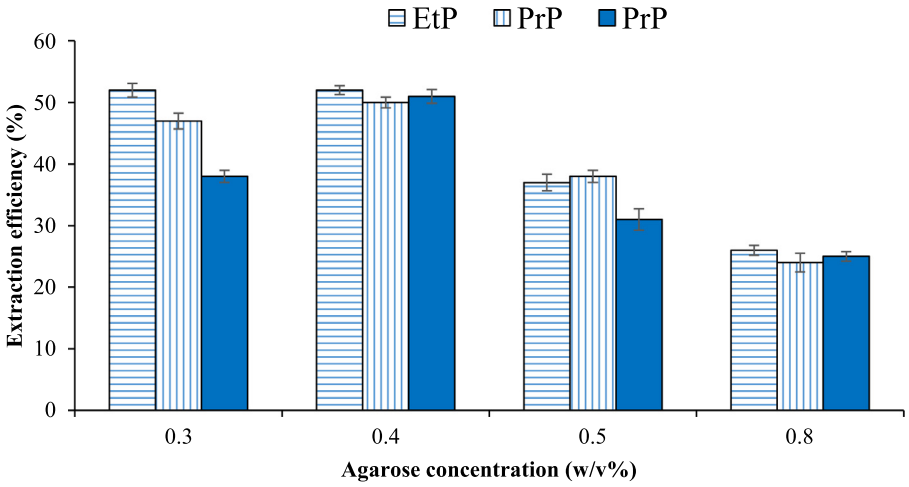

Fig. 3. Agarose concentration optimization.

different agarose percentage (0.3, 0.4, 0.5 and 0.8 v/w%) by impregnating each agarose membrane with 2 µL of Ca:Ty (2:1). Agarose membranes were prepared as described in our 2.3 section. As seen in Fig. 3, 0.4% offered the highest extraction efficiencies and it was fixed for further optimization. In parallel, a study was carried out using PP membranes selecting the optimal DES solvent obtained with the gel membranes, since previous studies [8] showed that the optimal solvents coincided when the optimization was carried out for both membranes individually. The results obtained using Ca:Ty (2:1) in PP membranes showed extraction efficiencies of 40, 47 and 48% for EtP, PrP and BuP, respectively. These data showed that the use of the biodegradable membrane combined with DES did not mean a decrease in the extraction efficiency and therefore, commonly used PP membrane could be substituted by gel membranes. On the other hand, microfluidic sample treatment systems typically use traditional (toxic) solvents on synthetic polypropylene supports, which have been shown to offer long-term SLM stability for consecutive extractions. Therefore, the stability of the SLM with Ca:Ty 2:1 was also carried out in order to compare the durability and stability of the system with respect to those commonly used in microfluidic platforms. Results showed that the new proposed Ca:Ty 2:1 as SLM allowed at least 10 consecutive extractions.

3.2. Optimization of the donor and acceptor composition

As mentioned above, diffusion coefficient is affected by the pH gradient between the donor and acceptor phases. In this way, donor and acceptor composition were also investigated within a pH range compatible with LPME requirements. Donor phase composition was studied between pH 1 and 6 to ensure the analytes in their neutral form. Each solution was adjusted using the HCl (1 mol L^{-1}) while the acceptor phase pH and the flow rates were kept constant at pH 12 and 1 µL min^{-1}, respectively. Based on the results (Fig. 4), the highest extraction efficiencies were obtained at pH 4 while for the rest of the pH values there is no significant difference, so this pH value was fixed as donor phase composition for the acceptor phase optimization. Acceptor phase pH was tested within a pH range 10–12.5 using NaOH (1 mol L^{-1}). As seen in Fig. 5, this variable is more critical than the composition of the acceptor phase, observing a more pronounced increase up to pH 12 and a significant decrease in the extraction efficiencies at a pH 0.5 points above pH 12. Therefore, pH 4.0 and pH 12.0 were selected as donor and acceptor phase composition, respectively, for extraction of parabens using gel membranes and Ca:Ty (2:1) as SLM.

3.3. Donor flow rate optimization

The sample flow rate was investigated within the range of 0.5–10 µL min^{-1} while the acceptor flow rate was fixed at 1 µL min^{-1}. The results are shown in Fig. 6. As expected, the extraction efficiency significantly decreased when the flow rate increased from 3 to 10 µL min^{-1} since the residence time of the sample and the contact analyte-SLM also decreased. On the other hand, no significant differences were observed between flow 0.5 and 1 µL min^{-1}, however, the extraction time is reduced by half when working at flow 1 µL min^{-1}. For this reason, 1 µL min^{-1} was selected as donor flow rate. Our previous studies demonstrated that the efficiency decrease when increasing the acceptor flow rate [10,23], then, acceptor flow rate was set at 1 µL min^{-1} to avoid a decrease in the extraction efficiency.

3.4. Geometry optimization

The geometry of the device was studied for both polypropylene and agarose membranes using DESs as SLMs in order to determine an increasement in extraction efficiency. For these experiments, optimal conditions were selected: pH 4 and pH 12 as donor phase and acceptor phase, respectively, 1 µL min^{-1} as donor and acceptor flow rates and Ca:Ty 2:1 as SLM. Regarding the geometry of the system, the mass transfer is slow under LPME conditions and shallower channels are preferred to avoid a decrease in extraction efficiency. As is known, the extraction of analytes under LPME conditions can be slow and depends on the analytes, membrane support and type of SLM so it is important to study the time in which the analytes are in contact with the membrane to improve passive diffusion. The residence time of the analytes along the microfluidic channel can increase or decrease depending not only on the flow but also on the length of the channels, so it is important to know how the diffusion capacity of these analytes is and if the time of residence is critical. This way, different geometries were tested, mainly varying the length of the extraction channel and keeping low depth at 70 µm. The following length (mm), width (mm) and depth (mm) sizes were compared: (a) 14 × 3 × 0.07, (b) 27 × 3 × 0.07, (c) 32 × 3 × 0.07 and (d) 40 × 3 × 0.07. With geometry (a), extraction efficiencies between 43–50% and 44–57% were observed for all compounds with PP and agarose membrane, respectively. For geometry (b), efficiencies between 40–61% and 53–69% were observed for PP and agarose membranes, respectively. When increasing the length with geometry (c) and (d), the efficiency did not increase. However, the extrac-

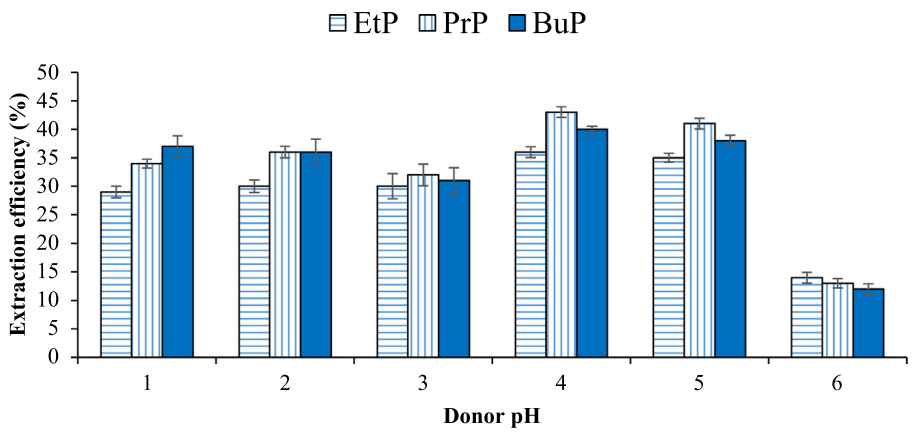

Fig. 4. Optimization of donor phase composition using agarose membranes. SLM: Ca:Ty (2:1), acceptor pH: 12, flow rate: 1 µL min^{-1} (acceptor and sample).

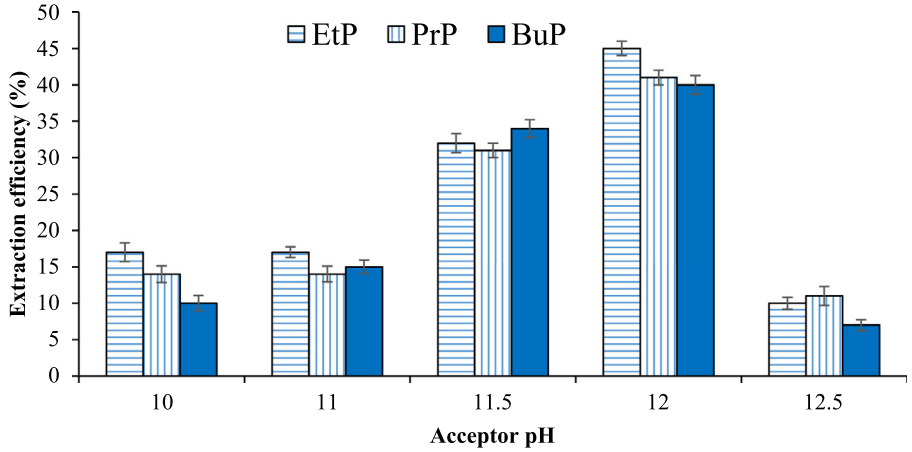

Fig. 5. Optimization of acceptor phase composition using agarose membranes. SLM: Ca:Ty (2:1), donor pH: 4, flow rate: 1 µL min^{-1} (acceptor and sample).

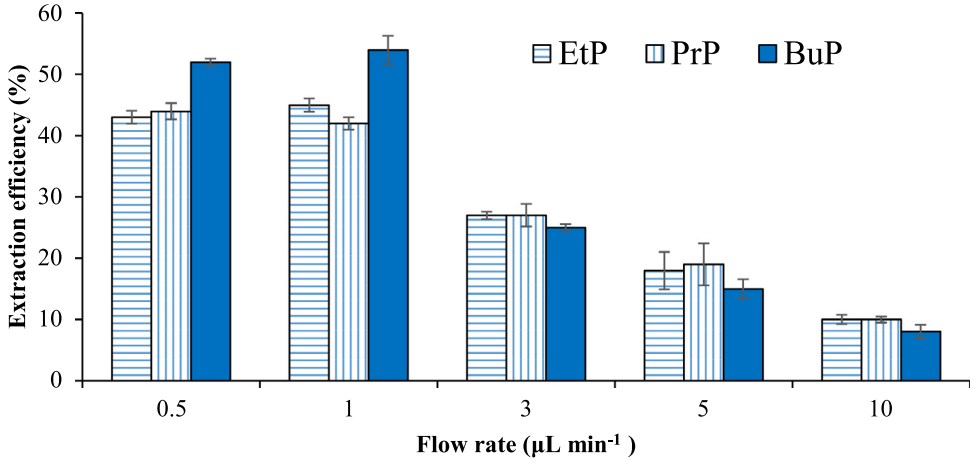

Fig. 6. Extraction efficiency versus sample flow rate. SLM: Ca:Ty (2:1), sample pH: 4, acceptor pH: 12, acceptor flow rate: 1 µL min^{-1}.

tion efficiencies were similar with both membranes when using different channel lengths. A slight increase was observed with geometry (b), so this microfluidic platform was selected for the rest of the study.

4. Analytical performance

Microfluidic method based LPME was evaluated for the determination of three parabens by fixing the experimental parameters at optimal conditions as described above. A calibration curve was constructed using a least-square linear regression analysis at seven different concentrations for the analytes in water. Table 2 summarize the linearity, repeatability, method detection limits (MLODs), and method quantitation limits (MLOQs) for each compound. The linearity range was 0.35–10 µg mL^{-1} for EtP, 0.38–10 µg mL^{-1} for PrP and 0.31–10 µg mL^{-1} for BuP, and the corresponding r^2 values exceeded 0.9995 in all cases. Limits of detection ($S/N = 3$) were 0.011, 0.013 and 0.093 for EtP, PrP and BuP, respectively; and Lim-

Table 2
Linearity, method detection limit (MLOD), method quantitation limit (MLOQ) and extraction efficiencies at optimal conditions.

	MLOD (μg mL^{-1})	MLOQ (μg mL^{-1})	Linearity range (μg mL^{-1})	R^2	EE(%)*
EtP	0.011	0.35	0.35–10	0.9997	64 (3)
PrP	0.013	0.38	0.38–10	0.9998	53 (5)
BuP	0.093	0.31	0.31–10	0.9995	69 (6)

* % Extraction efficiency (%RSD, $n = 4$) in water.

Table 3
Recoveries (average of three determinations ± standard deviation) from spiked urine samples at three different levels within the linear range.

Analyte	Concentration (μg/mL)	Volunteer 1 % Relative recovery (RSD%)	Volunteer 2 % Relative recovery (RSD%)	Volunteer 3 % Relative recovery (RSD%)
EtP	0.4	110 (7)	101 (4)	104 (6)
	1	103 (6)	97 (6)	96 (5)
	2.5	88 (5)	95 (6)	93 (5)
PrP	0.4	106 (6)	99 (3)	101 (5)
	1	95 (6)	97 (5)	96 (4)
	2.5	90 (4)	92 (6)	91 (5)
BuP	0.4	100 (5)	103 (6)	100 (3)
	1	98 (6)	98 (6)	99 (4)
	2.5	96 (4)	89 (4)	95 (4)

its of quantitation ($S/N = 10$) were 0.35, 0.38 and 0.31 for EtP, PrP and BuP, respectively. Repeatability ($n = 4$) and intraday repeatability ($n = 4$, 15 days) were tested at low, medium and high concentration levels within the linear range, and a relative standard deviation (RSD%) between 5–6% and 5–7% were obtained for repeatability and intraday repeatability, respectively. Under optimal conditions, the extraction efficiencies were 64%, 53% and 61% for EtP, PrP and BuP when using Ca:Ty 2:1 immobilized in agarose support membranes. RSDs were below 6% for triplicate experiments in all cases. Different devices were fabricated in order to check the reproducibility and each one was tested using different membranes and reusing several times the same one. The results showed RSDs values below 4% and 6% when using same or different membrane, respectively, in the same device. Also, good reproducibility was obtained using different devices with a%RSD<5.

5. Real samples analysis

The microfluidic method was applied in human urine samples collected from three different adult female volunteers (staff working in the laboratory). Each sample was treated under optimal conditions using gel membrane as support and Ca:Ty 2:1 as SLM. Non-diluted urine samples were spiked at three different concentration levels and the samples were submitted to the microfluidic device for analysis. Experiments were carried out in triplicate for each concentration level. As seen in Table 3, recoveries were between 91 and 100% in all cases within the three different levels. The efficiency slightly decreased when increasing the concentration level but no significantly. The device showed also reproducibility for at least 8 consecutive extractions when using human urine samples. A decrease in the extraction efficiency was observed after one and

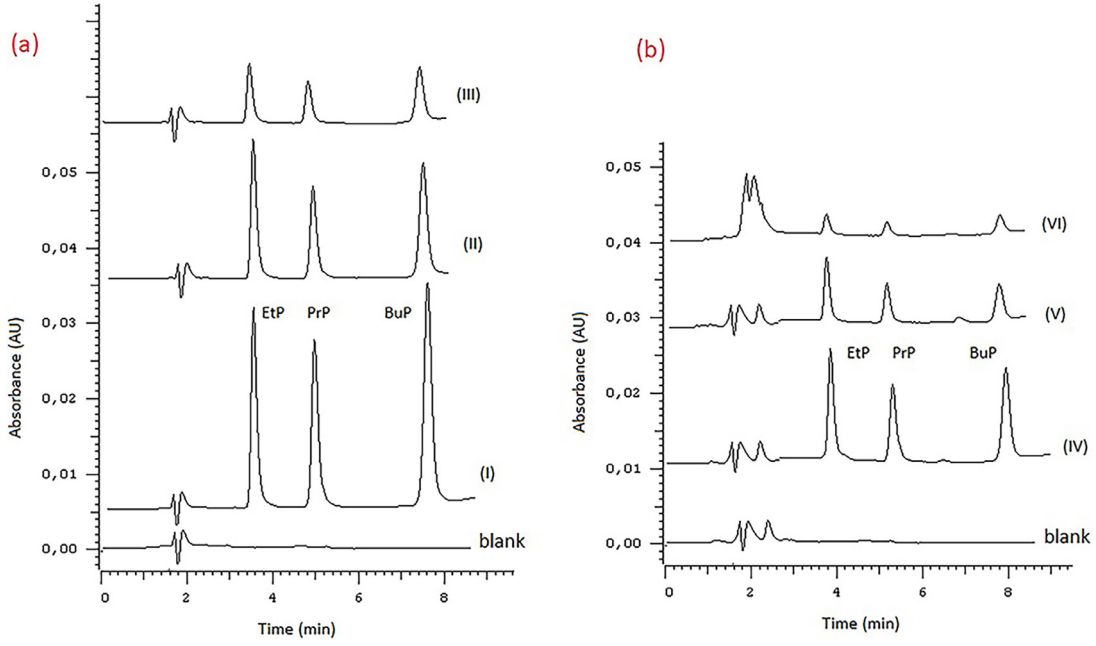

Fig. 7. Chromatogram of (a) a blank and standard solutions at 0.3, 0.9 and 1.5 mg L^{-1} and (b) a blank and spiked human urine samples at 0.3, 0.8 and 1.2 mg L^{-1}.

a half hours due to possible membrane clogging due to other interferences or components in the sample other than the analyte. Fig. 7 shows a chromatrogram for (a) standard solutions at different concentrations and (b) spiked urine samples at different concentrations. As seen in figure, the proposed microfluidic method based on green approaches offer an excellent clean-up.

6. Conclusion

This work has demonstrated a highly green microfluidic system based LPME in sample treatment. This miniaturized green system has been applied for the extraction of p-hydroxybenzoic acid esters (parabens). This system not only includes the fundamental advantages of microfluidic systems such as low volume of sample and reagents, short extraction times, reusability, the possibility to carry out consecutive extractions and portability; it also eliminates the use of toxic organic solvents by employing a deep eutectic solvent as the extraction phase. In addition, the possibility of immobilizing this natural solvent in a biodegradable agarose support provides great potential compared to other less environmentally friendly techniques. Furthermore, the efficiency observed was similar to that obtained when these DESs are immobilized on synthetic polypropylene supports. The good efficiencies obtained in real samples as well as their ease of application show that the use of these supports combined with deep eutectic solvents are an attractive alternative in sample treatment.

Ethics declarations

The sample was provided voluntarily and with informed consent.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Samira Dowlatshah: Formal analysis, Investigation, Data curation. **Mohammad Saraji:** Writing – original draft. **María Ramos-Payán:** Methodology, Conceptualization, Supervision, Writing – review & editing.

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