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Enhancing liquid phase microextraction enrichment in microchip devices under semi-stagnant conditions

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ABSTRACT

Liquid-phase microextraction (LPME) in microfluidic devices involves extraction of acids or bases by diffusion in a pH gradient, from aqueous sample, through a supported liquid membrane (SLM), and into aqueous acceptor phase. The SLM is an integrated part of the device, and separates the donor (sample) and acceptor phase channels. In this work, the geometry of the donor and acceptor phase channels were studied and optimized. With optimal channel geometry (12 mm length, 2 mm width, 0.12 mm depth), metoprolol, haloperidol, nortriptyline, and loperamide were extracted from 900 μL urine and into 25 μL stagnant 10 mM HCl using a mixture of dihexyl ether and tributyl phosphate 1:1 v/v as the SLM. During 30 min of extraction, where the sample was pumped into the system at 30 μL min^{-1} and the acceptor phase was stagnant, recoveries exceeded 75 % and enrichment factors up to 28 were obtained. Evaluation of the analytical performance supported the reliability of the device in combination with HPLC-UV detection. Implementation of LPME in microfluidic devices is expected to increase in the future and the current paper provides experimental support for the importance of the careful design of the donor and acceptor channels.

1. Introduction

Over the past decade, significant advancements have been made in the field of microfluidic devices, encompassing fabrication techniques, materials, integration, and applications [1–4]. Among the successful techniques implemented in microfluidic systems, liquid phase microextraction (LPME) [5,6] and electromembrane extraction (EME) [7–9] show potential. In LPME, bases or acids are extracted from aqueous sample, through a supported liquid membrane (SLM) and into aqueous acceptor phase. The driving force for mass transfer is a pH gradient sustained across the SLM. EME is similar, but the driving force is an electrical field sustained across the SLM.

In recent years, there has been extensive progress in the implementation of LPME and EME in microfluidics for sample treatment, aiming to enhance efficiency [10], reduce sample volume [11], minimize the use of hazardous solvents [12,13], decrease extraction time, improve its integration with different detection methods [14–18], and even using biodegradable membranes for microfluidic green approaches [19,20]. Initially, these systems were reported for the extraction of fluoroquinolones (acids) from urine by LPME and for the extraction of basic pharmaceuticals from a variety of biological fluids by EME [6,21,22]. Subsequently, efforts were directed towards the simultaneous extraction of acids and bases [23,24], and towards innovative geometric designs [25–27].

The geometry of microfluidic devices plays a crucial role in the performance of LPME and EME and can affect the efficiency and the enrichment factor. Under double-flow conditions, microfluidic LPME devices operate by introducing the acceptor and donor phase in parallel while in semi-continuous flow, the acceptor phase remains stationary [28,29]. One of the limitations of double-flow microfluidic systems is the limited enrichment factor, considering them an important limitation when the analyte is present in a low concentration in the sample. Only a few LPME and EME-based microfluidic systems have demonstrated enrichment under stagnant conditions [21,24,30,31].

Although the continuous advancement of miniaturized LPME and EME has brought about significant improvements in portability, cost reduction, and analysis efficiency, it remains crucial to address the limitations associated with these systems. In the current work, we study different geometries that specifically tackles the limitations related to low enrichments for the analysis of basic compounds of a wide range of

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polarity considering the sensitivity drawback in our previous double-flow microfluidic format [32]. We aim to contribute to the ongoing efforts to optimize microfluidic systems, improving their effectiveness and efficiency for a wide array of applications, particularly those requiring the extraction of analytes present at low concentrations in samples.

2. Experimental

2.1. Chemicals and sample solutions

All reagents and chemicals were of analytical grade. Metopropol (MTP), haloperidol (HLP), nortriptyline (NRP) and loperamide (LOP) were purchased from Sigma Aldrich (Madrid, Spain). 1-octanol, formic acid, methanol and chloride acid, were purchased from Fluka–Sigma–Aldrich (Madrid, Spain). Sodium hydroxide, 2-nitrophenyl octyl ether (NPOE), dihexylether (DHE), decanol, and tributyl phosphate (TBP) were supplied from Merck (Darmstadt, Germany). The stock solutions of basic compounds were prepared in methanol at 100 mg L^{-1} and storage at 4 °C. Working solutions were daily prepared from stocks solutions by adequate dilutions with deionized water (Milli-Q Plus water purification System). A micro-syringe pump (Cetoni GmbH, Korbussen, Germany) was used to introduce the donor phase into the device and a Celgard 2500 (25 μm thickness, 55% porosity, and 0.21 μm × 0.05 μm pores) was used as polypropylene fat membrane.

2.2. Design and set up of the microchip device

Fig. 1 shows the schematic representation of the microchip device. The poly(methyl methacrylate) (PMMA) device consisted of two distinct compartments for efficient sample treatment. One layer (referred to as layer 2) encompassed a channel with dimensions of 12 mm length, 2 mm width, and 0.12 mm depth. On the other hand, the second layer (referred to as layer 1) featured a hollow space measuring 12 mm length, 2 mm width, and 2 mm depth. The device was constructed using an Epilog Mini 24–30 W laser cutter. For the donor channel, the ablation conditions utilized were a writing speed and power of 35%, a resolution of 1500, and a frequency of 5000. As for the acceptor channel, different settings of 10% and 90% were employed for writing speed and power, respectively. The donor (sample solution) was introduced in the channel connecting two Teflon tubes with a diameter of 1.5 mm at the beginning and end of the channel. Layer 1 was located on top of the donor PMMA plate (layer 2) and a flat membrane (Celgard 2500) separated both channels. The device was assembled by utilizing four screws (3 mm o.d.) and the membrane was impregnated with 3 μL of 1:1 DHE:TBP. A micro-syringe pump (Cetoni GmbH, Korbussen, Germany) was used to introduce the donor solution. Once the extraction is completed, the acceptor solution was collected and subsequently analyzed by HPLC.

2.3. Chromatographic conditions

The HPLC separation was conducted using a VWR-Hitachi (Barcelona, Spain) liquid chromatograph equipped with a quaternary L-2130 pump and an autosampler L-2200 injector. A LiChroCART 75–4 Purosphere STAR RP-18e column (3 μm, 75 mm × 4.0 mm i.d.) (VWR, Germany) coupled with a guard column Kromasil1 100 Å, C18 (5 μm, 20 mm × 4.6 mm i.d.) (Scharlab S.L., Barcelona, Spain) was employed for the separation. The mobile phase consisted of 0.1% formic acid (pH 2.6) (component A) and methanol (component B) with a flow rate of 0.5 mL min^{-1}.

The separation program was adapted from a previously reported method [17]. Initially, an elution gradient was set as follows: from 100% to 60% A in 2 min and from 60 to 0% A (to 100% B) for another 16 min, maintained for 3 min, followed by a 5-minute re-equilibration at 100% A. The detection wavelengths were set at 200 nm for NRP, 220 nm for LOP, 250 nm for HLP and 280 nm for MTP. The total chromatographic run time was 18 min, and the retention times were 5.9, 10.6, 12.2 and 13.9 min for MTP, HLP, NRP and LOP respectively.

2.4. Preparation of spiked urine samples

Human urine samples were collected prior consent. Both, undiluted and 1:1 diluted urine samples were obtained from a healthy male volunteer aged 29 years. The model analytes were spiked into the urine samples at different concentration levels (0.1, 0.5, and 1 μg mL^{-1}) and

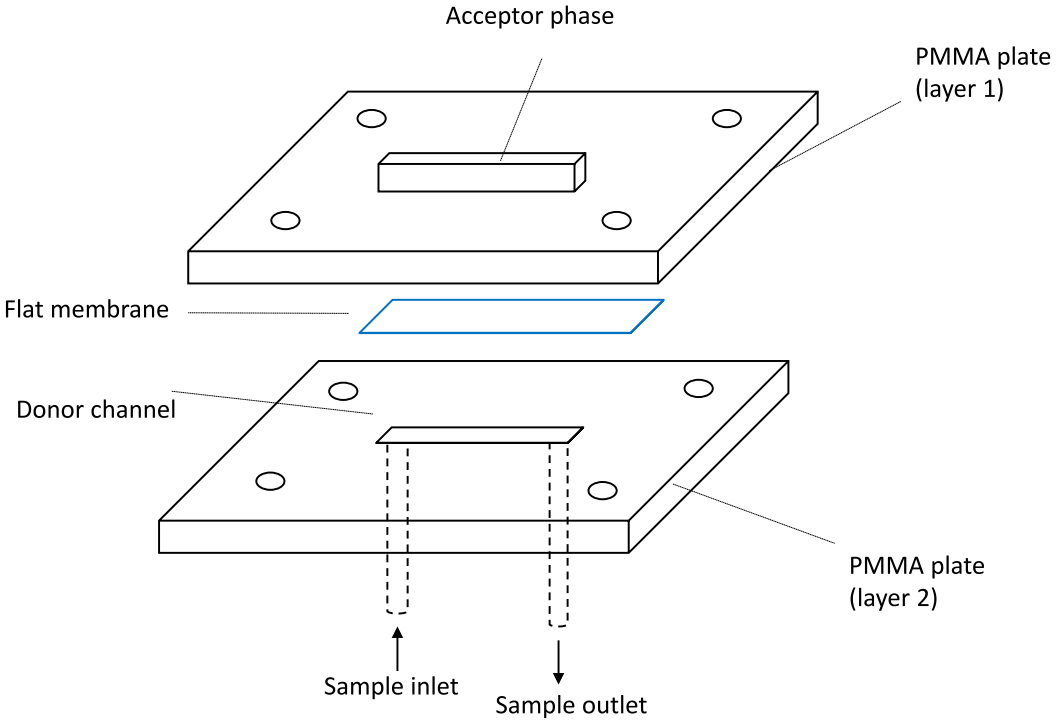

Fig. 1. Scheme of the semi-continuous microfluidic device.

all spiked urine samples were adjusted to pH 12 and filtrated using a Pall Nylaflo™ nylon membrane filter with a diameter of 32 mm and a pore size of 0.45 μm (Pall Corporation, Ann Arbor, MI, USA).

2.5. Calculations of extraction efficiency and enrichment factor

The enrichment factor (EF_i) for the analyte i was calculated according to the following Eq. (1):

$$EF_i = \frac{C_{f,a,outlet}}{C_{i,s,inlet}} \quad (1)$$

where $C_{f,a,outlet}$ is the concentration of the analyte i at the outlet of the acceptor channel and $C_{i,s,inlet}$ is the initial concentration of the analyte in the sample. $C_{f,a,outlet}$.

The extraction efficiency (EE %) was calculated according to the following Eq. (2):

$$EE(\%) = EF_i x \frac{v_a}{v_s} x100 \quad (2)$$

where $v_a and v_s$, are the acceptor and sample volume, respectively.

3. Results and discussion

3.1. Supported liquid membrane selection

The first series of experiments was focused on studying the composition of the supported liquid membrane (SLM). For these experiments, our previous device was used with stagnant acceptor phase and with the following channel size: 10 mm length, 2 mm width and 0.12 mm depth for the channel in the bottom layer, and a hollow of 6 mm length, 2 mm width and 2 mm depth for the top layer [31]. Five different organic solvents were selected as SLMs based on previous work for basic compounds [32]: 1-octanol, 1-decanol, NPOE, DHE, TBP and mixtures between those solvents. It is known that for the extraction of basic analytes by LPME, the compounds should be in their neutral form in the sample and positively charged in the acceptor phase. This allows the analytes to be extracted from the sample to the acceptor phase through the SLM. The experimental conditions were set based on the literature and the pKa values of the model analytes [33]. A pH 2.0 (10 mM HCl) was used as the acceptor phase, while a pH 12.0 (10 mM NaOH) spiked with model analytes was used as donor phase (containing 1 μg mL^{-1} of all model analytes). The donor flow rate was adjusted to 20 μL min^{-1}, and an extraction time of 15 min was employed. Our previous studies [11,31] demonstrated that increasing the donor flow rate enhanced enrichment both under double-flow and stagnant acceptor conditions. The volume of the acceptor phase was initially set at 15 μL.

The extraction efficiencies of the solvents were evaluated, and the results are summarized in Table 1. As seen in Table 1, TBP provided the highest extraction efficiency for MTP, whereas DHE provided the highest extraction efficiencies for the remaining model analytes. For this reason, DHE and TBP were mixed, and a 1:1 v/v ratio provided the highest extraction efficiencies. This finding was in agreement with previous work [32]. The pH stability was studied prior to and after extraction, with no significant changes. After each experiment, the membrane was replaced, and a new SLM of DHE and TBP 1:1 v/v was introduced.

Table 1
Extraction efficiencies (RSD %) of polar and non-polar basic compounds using different organic solvents as SLM.

SLM	Extraction Efficiency (%) ± SD (%)			
	MTP	HLP	NRP	LOP
NPOE	8 ± 3	21 ± 4	24 ± 4	31 ± 5
Decanol	18 ± 5	21 ± 6	27 ± 6	19 ± 4
TBP	31 ± 5	21 ± 3	29 ± 5	22 ± 4
Octanol	25 ± 6	20 ± 4	31 ± 2	17 ± 6
DHE	10 ± 5	24 ± 4	31 ± 3	38 ± 6
DHE - TBP 1:1	30 ± 5	25 ± 3	34 ± 4	47 ± 4
DHE - TBP 2:1	28 ± 5	23 ± 6	25 ± 3	38 ± 5
DHE - TBP 1:2	27 ± 3	21 ± 5	24 ± 4	31 ± 5

3.2. Study of the donor and the acceptor phase composition

The composition of both the donor phase and the acceptor phase plays a crucial role for the mass transfer, which relies on a pH gradient between the two phases. For these experiments, the donor flow rate and the extraction time were fixed at 20 μL min^{-1} and 15 min, respectively. First, the donor phase composition was studied within the range of 9.0–14 pH, keeping the acceptor phase composition fixed at pH 2.0. Under those conditions, the basic analytes were neutral in the donor phase and positively charged in the acceptor phase. As seen in Fig. 2, MTP and LOP showed the highest enrichment factors at pH 12, while pH 11 provided the optimal conditions for HLP and NRP. Donor phase at pH 12 was selected for the remaining experiments. Each experimental point was carried out in triplicate and a relative standard deviation below 4% was observed for all compounds. A pH range within 1.0–6.0 was studied for the optimization of the acceptor phase composition (Fig. 3). The optimal enrichment was achieved at pH 2.0 for all the model analytes. The basic analytes became fully protonated under low pH conditions, leading to increased ion-pair formation with phosphate, and partial back-extraction into the SLM. Therefore, an acceptor phase composition at pH 2.0 was selected for the subsequent experiments. All experiments were carried out in triplicate (n = 3), with a relative standard deviation below 3% for all the model analytes.

3.3. Study of the donor flow rate and extraction time

The donor flow rate was studied at different extraction times as seen in Table 2. The enrichment factor increased almost linearly when increasing the flow rate up to 30 μL min^{-1}, when the extraction time was kept constant. The same linear behaviour was observed upon increasing the extraction time up to 30 min, when the donor flow rate was kept constant. In both set of experiments, this was due to the increased volume of sample pumped into the device. Various combinations of donor flow rate and extraction time could be chosen according to the desired enrichments for analysing real samples and considering the available sample volume. The microfluidic system presented offers flexibility in terms of operation time and flow rates, tailored to meet the requirements of sample pre-concentration. By selecting a flow rate of 30 μL min^{-1} and an extraction time of 30 min, the system achieved high enrichment factors (EFs) ranging from 15 to 26 from only 900 μL of sample.

3.4. Study of the microfluidic device geometry

The geometry of the system was studied based on the length of the donor and acceptor channels, and the depth of the donor channel. This study was carried out with 30 μL min^{-1} as the donor flow rate and 30 min as the extraction time. New variations of the microfluidic system were fabricated by increasing the length of the donor channel from 10 to 12 mm, the length of the acceptor channel from 6 to 10–12 mm, and the depth of the donor channel from 0.12 to 0.20 mm. These variations were studied individually, manufacturing the following three new devices: (a) 10 mm as the length of both channels and 0.2 mm depth of the donor channel, (b) 12 mm as the length of the channels and 0.12 mm depth of the donor channel, and (c) 12 mm as channel length and 0.2 mm donor channel depth. A higher volume of acceptor phase (25 μL) was considered when increasing the length of the acceptor channel up to 10–12 mm. Extraction efficiencies and enrichment factors increased upon increasing the length of both channel as expected. This was due to an increase in the contact area of the SLM located between the donor and acceptor. Increasing the depth of the donor channel (a), slightly lower

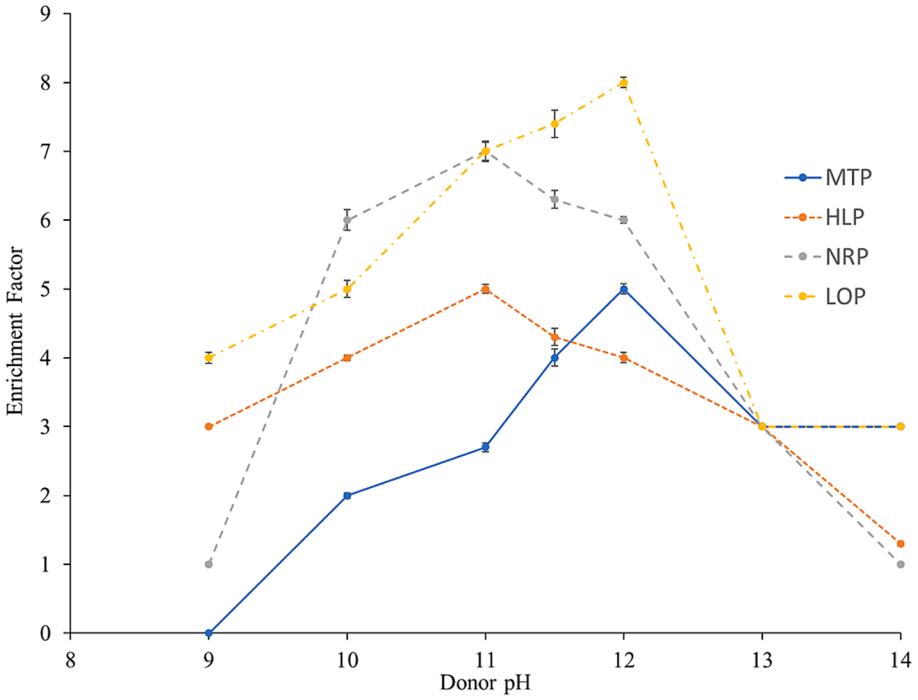

Fig. 2. Optimization of the donor phase composition. Experimental conditions: 1:1 DHE:TBP (as SLM), pH 2 (acceptor phase composition), 20 μL min^{-1} (donor flow rate) and 15 min (extraction time).

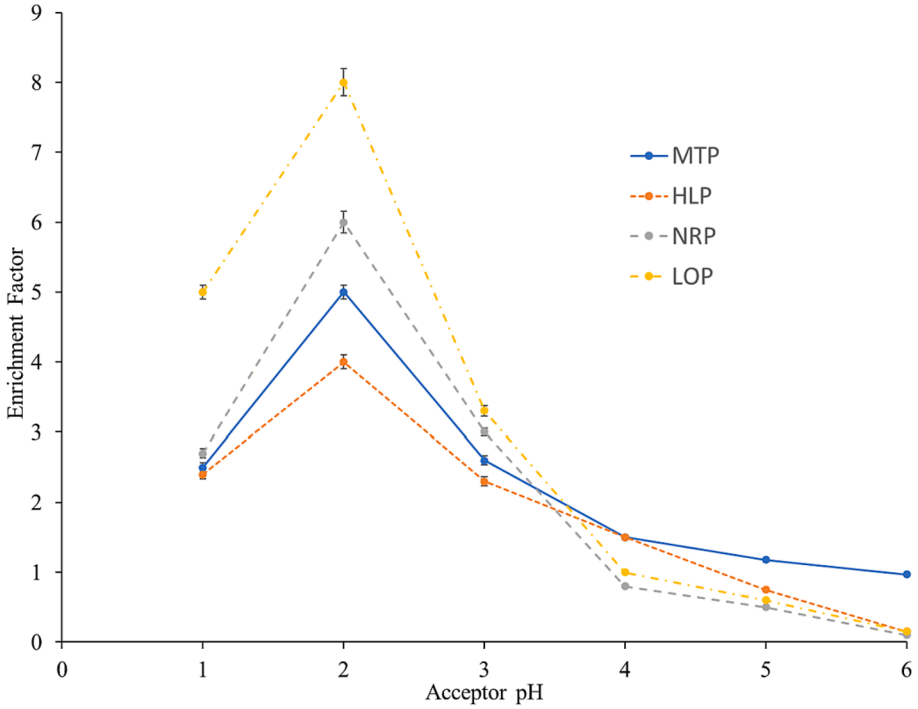

Fig. 3. Optimization of the acceptor phase composition. Experimental conditions: 1:1 DHE:TBP (as SLM), pH 12 (donor phase), 20 μL min^{-1} (donor flow rate), 15 min (extraction time).

EF (between 14 and 25) and extraction efficiencies (25–43%) were observed. Enrichment extraction between 18 and 28 and EE between 50 and 77% were achieve using device (b). Overall, the new device (b) showed the highest performance in terms of enrichment, and this device was used for the rest of the experiments. The stability of the SLM was assessed and investigated between devices during the extraction time selected. The results indicated a relative standard deviation (RSD) below 3%.

4. Evaluation of analytical performance

The performance of the microfluidic device was assessed for the simultaneous extraction of the basic model analytes from aqueous solutions. The experimental setup included a donor phase with a pH of 12,

Table 2
Enrichment factors at different donor flow rate and extraction times for all basic analytes selected.

Enrichment Factor*						
		Extraction Time (min)				
Analyte	Flow (μL min^{-1})	5	10	15	20	30
MTP	1	0.4	0.8	1.0	1.3	1.8
	5	0.7	1.6	2.3	3.1	3.8
	10	1.1	2.1	3.0	4.8	7.3
	20	2.8	3.9	5.3	7.2	11.9
	30	3.1	5.0	9.1	12.2	15.2
HLP	1	0.5	1.0	1.3	1.5	2.0
	5	0.7	1.1	1.7	2.4	4.1
	10	2.1	2.0	2.8	4.5	9.6
	20	3.3	3.2	4.4	9.2	17.3
	30	4.1	6.9	9.2	13.4	18.3
NRP	1	0.5	0.8	1.1	1.8	2.2
	5	1.8	2.1	2.0	2.9	5.1
	10	2.3	3.0	4.5	5.0	8.1
	20	4.1	5.9	6.7	11.1	14.3
	30	6.3	9.2	12.9	17.7	20.1
LOP	1	0.4	0.9	1.3	1.7	2,3
	5	0.8	1.0	2.0	2.9	4.9
	10	2.4	3.9	4.7	5.6	8.5
	20	3.9	7.2	8.8	12.5	17.4
	30	4.4	10.5	14.1	21.7	26.3

*RSD < 7% was obtained for all experiments.

an acceptor phase with a pH of 2.0, a mixture of 1:1 v/v DHE:TBP as the supported liquid membrane (SLM), a donor flow rate of 30 μL min^{-1}, and an extraction time of 30 min. A calibration curve was constructed using a least-square linear regression analysis within concentration ranges of 0.023 to 5 μg mL^{-1} for MTP, 0.023 to 5 μg mL^{-1} for HLP, 0.020 to 5 μg mL^{-1} for NRP, and 0.032 to 5 μg mL^{-1} for LOP. All analytes showed a linear relationship, with r^2 values over 0.9988. The detection limits, quantitation limits, linear ranges, regression coefficients, and enrichment factors for each analyte are summarized in Table 3. Three concentration levels (low, medium and high) within the linear range were tested in triplicate to study the inter-day and intra-day precision of the proposed method. Inter-day and intra-day precision were within 2.0 and 4.0 % RSD, respectively. In both studies, the SLMs were replaced for each experimental point. Enrichment factors can vary depending on the selected operational parameters regarding donor flow rate and extraction time under stagnant conditions. Enrichment factors between 18 and 28 were obtained for the model analytes under the selected operational parameters (donor flow rate of 30 μL min^{-1}, and 30 min extraction).

5. Urine samples analysis

The microfluidic method was finally applied for human urine samples. Urine samples were collected from a healthy adult male volunteer prior consent. The pH of both non-diluted and diluted (1:1) samples with miliQ water was adjusted to pH 12. Subsequently, the samples were spiked with three different concentrations within the calibration curve for each analyte. Table 4 shows the results, observing spiking recoveries between 63 and 80% and 73–92% for non-diluted and diluted (1:1) samples, respectively. Spiked recovery data was calculated comparing the results of each compound in urine samples and aqueous solutions after the extraction. Fig. 4 shows the chromatograms corresponding to (A) spiked urine samples containing all analytes and (B) blank urine sample after microfluidic extraction, observing an excellent clean-up under stagnant conditions of the acceptor phase.

Table 3
Calibration parameters, detection limit (LOD), quantitation limit (LOQ) and enrichment factors at 30 μL min^{-1} and 30 min extraction.

	LOD[a] (μg mL^{-1})	LOQ[a] (μg mL^{-1})	$R^{2,a}$	Linear range[a] (μg mL^{-1})	EF [*,a]
MTP	0.007	0.023	0.9992	0.023–5	18 (1)
HLP	0.007	0.023	0.9991	0.023–5	22 (2)
NRP	0.006	0.020	0.9988	0.020–5	23 (1)
LOP	0.013	0.032	0.9993	0.032–5	28 (3)

[*] Enrichment factor (%RSD, n = 3).
[a] Extraction at 30 μL min^{-1} donor flow rate and 30 min extraction. Sample volume consumption: 900 μL.

6. Conclusions

For the first time, the geometry of a semi-continuous microfluidic device for liquid-phase microextraction (LPME) has been studied and optimized with respect to analyte enrichment. Increasing the length of the donor and acceptor channels increased the contact area with the supported liquid membrane, and this increased both the extraction efficiency and the enrichment performance of the system. Increasing the depth of the donor channel, on the other hand, decreased the extraction efficiency. With optimized donor and acceptor channel geometry, a selection of basic drugs in the log P-range 1.75 < log P < 5.13 were extracted from human urine samples. Spiking recoveries exceeded 75 % for all substances, and enrichments up to 28 times were obtained from 900 μL urine samples. Due to proper design of the microfluidic channels, the extraction system was highly efficient for analytes in a large polarity range. Implementation of LPME in microfluidic devices is expected to increase in the future, and the current paper provides experimental support for the importance of optimization of the donor and acceptor channel dimensions.

7. Ethics declarations

Samples were provided voluntarily and with informed consent.

CRediT authorship contribution statement

Alejandro Martín: Formal analysis, Investigation, Validation. **Samira Dowlatshah:** Writing – original draft, Visualization. **Stig Pedersen-Bjergaard:** Writing – original draft. **María Ramos-Payán:** Conceptualization, Methodology, Supervision, Funding acquisition, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

Table 4
Recoveries (average of three determinations ± standard deviation) from spiked urine samples at different concentrations.

Urine Samples	Concentration level (μg mL^{-1})	Recovery (%) ± SD (%) (n = 3)			
		MTP	HLP	NRP	LOP
Non-diluted	0.1	64 ± 2	77 ± 2	78 ± 2	67 ± 3
	0.5	63 ± 2	78 ± 1	75 ± 3	63 ± 3
	1.0	67 ± 3	76 ± 2	80 ± 1	65 ± 2
1:1 dilution	0.1	79 ± 1	82 ± 2	96 ± 2	73 ± 3
	0.5	77 ± 3	85 ± 1	89 ± 1	74 ± 2
	1.0	81 ± 1	84 ± 3	92 ± 1	75 ± 2

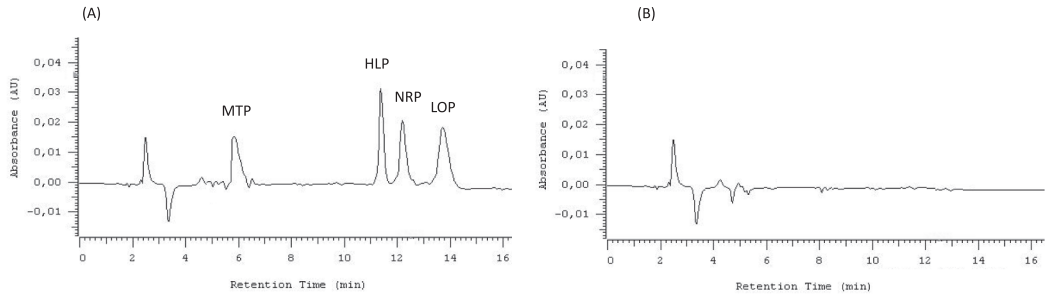

Fig. 4. Chromatogram of a (A) spiked urine sample after microfluidic extraction containing all analytes and (B) blank urine sample after microfluidic extraction.

the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgements

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