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Abstract: The use of polymer inclusion membranes (PIMs) as support of 1-octanol liquid membrane in electromembrane extraction (EME) procedure is proposed. Synthesis of PIMs were optimized to a composition of 29% (w/w) of cellulose triacetate as base polymer and 71% (w/w) of Aliquat®336 as cationic carrier. Flat PIMs of 10 □m thickness and 6 mm diameter were used. EME protocol was implemented for the simultaneous extraction of four non-steroidal anti-inflammatory drugs (NSAIDs) (salicylic acid, ketoprofen, naproxen and ibuprofen) and four highly polar acidic drugs (anthranilic acid, nicotinic acid, amoxicillin and hippuric acid). Posterior HPLC separation of the extracted analytes was developed with diode array detection. Recoveries in the 81-34% range were obtained. EME procedure was applied to human urine samples.

Use of Polymer Inclusion Membranes (PIMs) as support for electromembrane extraction of non-steroidal anti-inflammatory drugs and highly polar acidic drugs

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Abstract

The use of polymer inclusion membranes (PIMs) as support of 1-octanol liquid membrane in electromembrane extraction (EME) procedure is proposed. Synthesis of PIMs were optimized to a composition of 29% (w/w) of cellulose triacetate as base polymer and 71% (w/w) of Aliquat®336 as cationic carrier. Flat PIMs of 10 μm thickness and 6 mm diameter were used. EME protocol was implemented for the simultaneous extraction of four non-steroidal anti-inflammatory drugs (NSAIDs) (salicylic acid, ketoprofen, naproxen and ibuprofen) and four highly polar acidic drugs (anthranilic acid, nicotinic acid, amoxicillin and hippuric acid). Posterior HPLC separation of the extracted analytes was developed with diode array detection. Recoveries in the 81-34% range were obtained. EME procedure was applied to human urine samples.

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1. Introduction

Polymer Inclusion Membranes (PIMs) are homogeneous, self-supporting membranes usually composed of an extractant (carrier), a base polymer, commonly polyvinyl chloride (PVC) or cellulose triacetate (CTA), and a plasticizer or modifier. The mechanical strength of the membrane, as well as its diffusive resistance, is provided by the base polymer. The carrier is essentially an ion-exchanger or a complexing agent, which binds with the species of interest, transporting them across the PIM. The concentration gradient of the species/carrier complex or ion-pairs formed within the membrane is the responsible of the species transportation through the membrane. Plasticizer, not only provides the membrane with elasticity and flexibility, but also acts as solvent. The presence of plasticizer also improves the compatibility of the membrane components [1-2]. Carrier also acts as a plasticizer in some cases, so an additional plasticizer is not necessary. Another component (a modifier) can be occasionally added to the PIM composition in order to improve the solubility of the extracted species in the membrane liquid phase.

Polymer-based membranes have been used since long ago as an important alternative to traditional solvent extraction, however, in the last years their applications have been focused on chemical sensing, acting as ion-selective electrodes (ISEs) [3]. Composition of PIMs is essential on their physical and chemical properties as well as on membrane selectivity. Several researchers have been studying the transport efficiency through PIMs. It is known that the nature and components of PIMs improve the transport of the target species through the membrane, making it faster [4]. Another advantage of these kinds of membranes is that the entire membrane is available for ion transport. These characteristics, between others (easy operation, minimum use of hazardous chemicals, flexibility) make PIMs more advantageous membranes compared with the traditional supports for liquid membranes (SLM). Consequently, in the literature several researches about the use of PIMs as alternative membranes in electro-membrane extraction (EME) can be found. It has been probed their efficiency for the extraction of inorganic and organic anions (propanesulfonate, heptanesulfonate, decanesulfonate, tetraethylammonium, tetrabutylammonium and tetrapentylammonium) [4-8].

In the last years, some technical developments in EME have been published [9]. Within this realm, new supports for liquid membranes in EME procedures have also been proposed and implemented as available and advantageous alternatives to traditional polypropylene supports: carbon nanotubes [10-11], hollow polymer inclusion membranes [12] or nanostructred supports of diverse nature [13-14]. Our research group has recently been investigating in the development of new nanostructured supports for EME as real and promising alternatives to polypropylene hollow fibers or flat membranes.

Román-Hidalgo et al [13] proposed agarose films containing silver nanoparticles as new supports for EME of non-steroidal anti-inflammatory drugs (NSAIDs). In this research, the new support acts as active part in the extraction process of the analytes.

Another new support was proposed by researchers belonging to our group [14] for carrier-mediated electromembrane extraction of highly acidic polar compounds (nicotinic acid, amoxicillin, hippuric acid and salicylic acid). In this case, the new

support for SLM in EME consisted of an acrylic nanofiber membrane sheet (100 µm thickness) containing high density of –OH groups.

In the present work, the use of PIMs as support for EME is proposed for the simultaneous extraction of four NSAIDs (salicylic acid (SAC), ketoprofen (KTP), naproxen (NAX) and ibuprofen (IBU)) and four acidic polar drugs (hippuric acid (HIP), anthranilic acid (ANT), amoxicillin (AMX) and nicotinic acid (NIC)). 1-octanol as SLM is supported in a synthesized homogeneous flat sheet PIM of CTA in DCM with Aliquat®336 as cationic carrier. EME is carried out in a self-made device using HPLC for the determination of the target analytes.

The four selected NSAIDs belong to a wide group of compounds known due to their anti-inflammatory, analgesic and antipyretic properties. These drugs work by blocking cyclo-oxygenase (COX) enzymes, though NSAIDs can have different chemical structures [15]. On the other hand, among the acidic polar drugs, HIP is one of the major urinary endogenous metabolites on humans, population submitted to toluene intoxication [16] or with renal failures [17] can show high concentrations of this compound in urine. NIC, which is the common form of the B3-vitamin being one of the essential human vitamins [18]. ANT is an intermediate in the metabolism of tryptophan, being endogenous in humans [19].

EME procedures for the extraction of NSAIDs, as well as for acid and basic drugs, have been developed using different supports for SLM (agarose films containing silver nanoparticles, nanofiber membranes or decorated hollow fibers, among others) [13-14, 20]. Nevertheless, to our knowledge it is the first time that simultaneous extraction of high polar drugs together with NSAIDs using EME has been done. This is a noticeable advantage of the proposed protocol due to the different characteristics and properties of the selected molecules. Good recoveries (%) are obtained for all the extracted compounds. Besides, the method has been successfully applied to the determination of the target analytes in human urine samples.

2. Experimental

2.1. Chemicals and reagents

All chemicals and reagents were of analytical grade. Hippuric acid (HIP) and anthranilic acid (ANT) were obtained from Alfa Aesar (Karlsruhe, Germany). Amoxicillin (AMX), nicotinic acid (NIC), salicylic acid (SAL), 1-octanol, dihexyl ether, cellulose triacetate (CTA), nitro-phenyl-octyl-ether (NPOE) and Aliquat®336 were obtained from Fluka-Sigma-Aldrich (Madrid, Spain). Ketoprofen (KTP), naproxen (NAX), ibuprofen (IBU), sodium hydroxide, hydrochloric acid, acetic acid, sodium acetate, sodium dihydrogen phosphate, ammonia, dichloromethane, methanol, ammonium chloride and tris(2-ethylhexyl)phosphate were obtained from Merck (Darmstadt, Germany). 2-ethylnitrobenzene and heptanol were obtained from VWR (Darmstadt, Germany). Dimethylformamide (DMF) was obtained from Panreac (Barcelona, Spain). Ultrapure water from Milli-Q Plus water purification system (Millipore, Billerica, MA, USA) was used for preparing all solutions and dilutions. Working solutions were daily prepared by adequate dilutions from aqueous solutions

(400 mg L^{-1}) of NIC, AMX, HIP and ANT. In the case of SAL, KTP, NAX and IBU, dilutions were prepared from methanolic 400 mg L^{-1} solutions.

2.2. PIMs preparation

The preparation of the flat sheet membrane was based on the protocol proposed by See et al. with several modifications [5-6]. The synthesis was as follows: 0.6 g of cellulose triacetate (CTA) was added to 30 mL of dichloromethane, the mixture was placed in an ultrasonic bath till complete solution. On the other hand, the amount of Aliquat®336 corresponding to a 5% (w/v) in the final mixture was weighted and added to the CTA solution. After homogenization, 2.5 mL of the resulting mixture were poured onto a glass (90 mm diameter) Petri dish and dichloromethane was allowed to evaporate slowly at room temperature. Once the solvent was completely evaporated, membranes (10 μm thickness), containing 29% (w/w) CTA and 71% (w/w) Aliquat®336, can be peel off the dishes.

2.3. EME proposed procedure

EME procedure for the extraction of the selected analytes was developed according to a home-made device previously designed in our laboratory for carrier-mediated EME of polar compounds using nanostructured supports for SLM [13]. In this case, the synthesized PIM described above has been used as support. 10 mL (pH 4) of donor phase containing the target analytes in a concentration of 1 mg L^{-1} was placed in a 25 mL glass vial. The compartment used for acceptor solution was a screw plug 2 mL 2-SV glass micro vial (Chromacol, Welwyn Garden City, UK). Previously, the bottom of this micro vial was cut, placing the PIM in the micro vial plug and screwing it in order to seal the compartment by pressure. The micro vial, sealed with the plug (containing the PIM) was soaked in the organic solvent (1-octanol). Now, the micro vial was put upside down in order to fill it with 300 μL of acceptor phase (300 μL, pH 10). Platinum electrodes (0.25 mm diameter) ending in spiral shape were placed into both, acceptor and donor phases. Both electrodes were connected to a Power Source 300V DC power supply (VWR International, West Chester, Pennsylvania, USA) with programmable voltage in the range 2-300 V, providing currents in the range 4-500 mA. The described device can be seen in Figure 1.

50 V was applied during 30 min with the donor phase stirring at 300 rpm. The average current registered during the extraction time was in the range 100-1000 μA. Once EME was carried out, 20 μL of the acceptor phase were collected with a microsyringe and injected in the HPLC system.

2.4. Chromatographic conditions

A LabChrom® VWR-Hitachi (Barcelona, Spain) liquid chromatograph was used for the HPLC separation of the analytes. The system was equipped with a quaternary L-7100 pump and a L-7455 diode array detector (DAD). A L-2200 autosampler was used for the injection of the samples (20 μL). A LiChroCART® 75-4 Purosphere® STAR RP-

18e 3 μm (75 mm×4.0 mm i.d) (VWR, Darmstadt, Germany) column, with a Kromasil® 100 Å, C18, 5 μm (15 mm×4.6 mm i.d.) (Schrarlab S.L., Barcelona, Spain) guard column, was used for the chromatographic separation. Column was thermostated at 20°C during the separation time.

Gradient elution was used at a flow rate of 0.8 mL min^{-1}, using as mobile phase 0.05% aqueous formic acid (component A) and acetonitrile (component B). Initial conditions are 99% (v/v) A, decreasing to 90% in 3 minutes, maintaining this rate 1 min, then the rate decrease to 60% in 0.1 minutes, maintaining it for 12 min. Finally, %B (v/v) increases till 100% in 7 minutes. The monitoring wavelengths for DAD detection were 260 nm for NIC, 230 nm for AMX, 235 nm for HIP, 224 nm for ANT, 235 nm for SAL, 255 nm for KTP, 230 nm for NAX and 224 nm for IBU, respectively.

3. Results and discussion

3.1. Preliminary assays

All the preliminary EME assays were carried out using 10 mL of a standard aqueous solution containing the target compounds (1 mg L^{-1}) as donor phase and 300 μL of an aqueous solution as acceptor phase.

3.1.1. Optimization of the PIM synthesis

As it was mentioned in section 2.2., PIM was synthesized dissolving a certain amount of CTA in DCM and mixing this solution with Aliquat®336. According to the literature, plasticizer or modifier can also be present in the membrane [1-2]. Consequently, preliminary assays were carried out in order to synthesize a PIM with optimal properties as support of SLM in EME purposes. Different amounts of CTA (75-600 mg) were dissolved in variable volumes (20-30 mL) of DCM. In order to get the better physical properties of the resulting PIM, in terms of thickness and flexibility, as well as for obtaining better recoveries of the selected analytes, the optimal proportion for this solution was 600 mg of CTA dissolved in 30 mL of DCM.

Besides, different proportions of tris(2-ethylhexyl)phosphate (TEHP) as plasticizer (0, 2.5, 5 and 10% (w/v)) were tested. The presence of plasticizer conditioned the elasticity of the membrane as well as its consistence. When plasticizer was added to PIM, the resulting membrane had a poor consistence. Thus, this component was not used in the membrane synthesis.

The presence of different amounts of carrier in the composition of the PIM was also tested. The proportion of carrier in the membrane was an important fact, especially due to the role that this component plays in the carrier-mediated EME procedure of the target analytes. Therefore, the presence of Aliquat®336, as cationic carrier, in the composition of PIM was studied. Different proportions (0, 1, 2.5, 5, 7 and 10% (w/v)) of this carrier in solution were checked. Due to the chemical structure of the analytes, the presence in the membrane of Aliquat, favors the carrier-mediated extraction of the compounds. When the proportion of Aliquat was lower than 5%, obtained recoveries were poor (10-15%, for all the compounds). For 5% Aliquat, recoveries ranging 34-81% were obtained. Nevertheless, for higher proportions of Aliquat (>5%), the obtained

recoveries ranged between 10-35%. Thus 5% (w/v) of Aliquat®336 in PIM led to better yield in terms of extraction.

Once the proportions of CTA and Aliquat®336 were optimized, the synthesis of the polymer inclusion membrane was set by dissolving 0.6 g of CTA in 30 mL of DCM, once homogeneous, the amount of Aliquat®336 corresponding to a 5% (w/v) was weighted and added to the CTA solution till homogeneous mixture.

Finally, in order to synthesize membranes of different thickness, variable volumes (2.5, 5 and 10 mL) of the homogeneous mixture were poured out into Petri dishes. After complete evaporation of the solvent, membranes of 25-80 μm thickness were respectively obtained. A Zeiss Auriga Scanning Electron Microscopy (SEM) was used in order to get the exact thickness of the resulting PIMs. Thickness of 25.6-27.4, 49.5-51.0 and 79.6-81.0 μm were respectively measured in each of the synthesized PIMs. After applying the EME procedure using PIMs of the three thicknesses, it was checked that thicker PIMs only led to poor recoveries ranging 2-10% for all the compounds. Nevertheless, thinner PIMs were those that led to better extraction recoveries for all the target analytes. When analytes have to cross a thinner support, the extraction and thus, obtained recoveries are better. Therefore, once the solvent was completely evaporated, the optimal PIM composition in terms of recoveries was 29% (w/w) CTA and 71% (w/w) Aliquat®336. Figure 2 shows the SEM image corresponding to the thinner PIM.

3.1.2. Organic solvent as SLM

Different organic solvents were tested as SLM: 1-octanol, dihexyl ether, 2-ethylnitrobenzene, heptanol, nitrophenyl-octyl ether (NPOE) and dimethylformamide (DMF). DMF was rejected due to the fact that PIM nature was affected by this solvent. No appreciable differences, in terms of enrichment factors, were obtained for the rest of solvents. Consequently, 1-octanol was selected as SLM according to the good results, in terms of enrichment factors, achieved in previous EME procedures carried out in our group [12-13, 21].

3.2. Influence of pH of donor and acceptor phases

According to previous studies, pH of both acceptor and donor phases is one of the experimental parameters that should be controlled due to its importance in EME performance. Slampová et al. established quantitative aspects of electrolysis in electromembrane extractions [22-23]. Kubán et al. also contributed to this aspect with some important considerations on pH control of acceptor solution during EME process [24]. Besides, during the time of extraction, the presence of electrolytic generated OH^- and H^+ affects pH of acceptor and donor phases. This fact is highly dependent on applied voltage, time of extraction and nature of the compounds that migrate in EME procedure. Therefore, pH control should be done in order to implement the extraction yield.

Consequently, several EME experiences were carried out controlling pH of both, acceptor and donor phases. These experiments were done during 10 minutes and applying 50V. Five different pH values in the acceptor phase were tested: 2, 4, 6, 10 and 12. Acetic acid solution (5.69 M) was used for achieving pH 2. 100 mM acetate/acetic

buffer was used for adjusting pH 4 and pH 6. pH 10 was adjusted using a 100 mM ammonium chloride/ammonia buffer and pH 12 was achieved with ammonia solution (100 mM). When EME procedure was carried out at pH 2, very low recoveries were obtained for all the compounds. Figure 3 shows the recoveries obtained for the extractions developed for the rest of pH values. As it can be seen, recoveries increase with pH value reaching a maximum at pH 10 for most of analytes, decreasing the recoveries for higher pH. This fact can be explained according to the pK_a values of the compounds. NSAIDs are mostly in ionic form from pH 5. High polar drugs are also in ionic form at higher pH values, which favours their extraction as ion pair. Thus, pH 10 was the optimal value selected for pH of the acceptor phase.

In the same way, pH value of the donor phase was optimized. In all cases, pH of the acceptor phase was adjusted at pH 10 using a 100 mM ammonium chloride/ammonia buffer. Different values of pH (4, 6 and 10) for donor solution were tested. In the case of pH 4, this was the resulting pH of the analytes solution. For adjusting pH 6 and pH 10, buffers mentioned above were also used. When EME was carried out using pH 6 and 10 in donor phase, neither volume nor pH value kept constant during the extraction procedure. Therefore, pH 4 was set at the optimal pH value for donor phase.

3.3. Optimization of applied voltage and time of extraction

Once implemented pH values of acceptor (pH 10) and donor phase (pH 4), another experimental variable that was optimized was the applied voltage during EME procedure. Voltages in the range 10-100V were tested. All the experiments were carried out adjusting pH 10 for acceptor phase and pH 4 for donor phase. In Figure 4, the obtained recoveries for all the target analytes are depicted at the different applied voltages. It is noticeable that recoveries increased with the applied voltage from 10V to 50V. From this voltage, recoveries decrease slightly or keep their values constant till 100V. Accordingly, 50V was selected as applied voltage during EME process.

In order to optimize the time of extraction, EME was carried out during 5, 10, 15, 20, 25, 30, 35 and 40 min, respectively. In all the extractions the applied voltage was 50V. Obtained results, in terms of recoveries (%), can be seen in Figure 5. In the range 5-10 min, recoveries of all the analytes increased. In the range 10-30 min, there is variability in the obtained recoveries, though the values of recoveries increased for all the analytes. For times of extraction higher than 30 min, recoveries decreased in all cases. Thus, 30 min was the selected time for developing EME procedure.

3.4. Influence of acceptor/donor phases volume

Volume ratio of acceptor/donor solutions was also optimized. Due to the design of the device in which EME was carried out, volumes higher than 300 μL of acceptor phase were not available. Thus, different volumes of donor solution were studied. 5, 10, 15 and 20 mL were tested. Better results in EME were obtained using 10 mL.

Consequently, after implementing all the experimental variables described above, EME process was carried out as described in section 2.3.

3.5. Validation of the EME procedure

After carrying out EME procedure according to the optimal experimental conditions, the obtained recoveries for the target analytes were: 81% for NIC, 52% for AMX, 78% for HIP, 34% for ANT, 50% for SAL, 35% for KTP, 48% for NAX and 37% for IBU, respectively. Thus, PIMs can be successfully used as support for simultaneous electromembrane extraction of NSAIDs and acidic polar drugs.

A validation process was carried out in order to confirm the suitability of the proposed EME procedure. As quality parameters, linearity, sensitivity, precision and recovery were studied.

Matrix effect due to the presence of urine samples was observed, thus standard addition was used for the calibration. In Table 1, calibration data of the chromatographic method can be seen. Also, linear range as well as limit of detection (LOD) and limit of quantitation (LOQ) are depicted for all the target analytes, according to the effective recovery. The criteria used for LOD and LOQ calculation was the signal to noise ratio (3 for LOD and 10 for LOQ, respectively) [25]. Good linearity is obtained for all the studied compounds, ranging the linearity (%) between 96.0 for KTP and 98.0 for SAL. Values ranging between 18.0 μg L^{-1} for SAL and 100.0 μg L^{-1} for AMX were obtained for LODs. LOQs range between 61.0 μg L^{-1} for SAL and 333.3 μg L^{-1} for AMX.

The EME proposed method was applied to urine samples in order to evaluate the repeatability and intermediate precision. Measurements were done in one single day and two days per week during three weeks, respectively. The obtained values for %RSD were 1-8 % for repeatability and 2-12% for intermediate precision, respectively.

After the validation study, it can be assessed that the use of PIMs as support for SLM is adequate for the simultaneous electromembrane extraction of NSAIDs and highly polar drugs.

3.6. Application to real samples

In order to study the application of the EME proposed protocol to real samples, NAX, AMX, IBU and SAL were selected for being determined in human urine samples. These four drugs are the active ingredient of tablets (containing different doses), which can be easily acquired by population in chemits´s.

According to the literature, 60% of the oral ingestion of AMX is excreted by urine in a period of 6-8h [26]. In the case of NAX, 95% approximately of this drug (from any dose) is excreted in the urine, being 66-92% as conjugates, <1% as 6-0-desmethyl-naproxen and <1% as NAX [27]. The usual dosage of IBU, supplied as tablets, is 400-800 mg three times a day. This drug is completely eliminated in 24 hours after the last dose. In a period of 6-8h after the ingestion approximately 10% is excreted by urine. More than 90% of an ingested dose of IBU is excreted in the urine as metabolites or their conjugates, being the major metabolites hydroxylated and carboxylated compounds [28-29]. On the other hand, after administration of acetylsalicylic acid (ASA), SAL is generated by hydrolysis [30]. Usual SAL urine levels are in the hundreds of μg mL^{-1} range [31].

Therefore, human urine collected from healthy volunteers after the administration of different oral doses of NAX, AMX, ASA and IBU were microfiltered (0.22 μm), diluted with ultrapure water (1:500, v/v) and submitted to the EME procedure. Figure 6 shows the chromatograms corresponding to (a) human urine sample spiked at 500 μg L^{-1}; (b) human urine sample collected 3h after an oral administration of 550 mg of naproxen; (c) human urine sample collected 7h after an oral administration of 600 mg of ibuprofen (d) human urine sample collected 7h after an oral administration of 750 mg of amoxicillin; (e) human urine sample collected 4h after an oral administration of 500 mg of acetylsalicylic acid. All chromatograms show good baselines and well-defined peaks for the target analytes.

Once carried out the EME procedure in the human urine samples, the obtained results can be seen in Table 2. Taking into account the collected volume of urine as well as the effective recovery of the EME procedure (Table 2) for each of the analyzed drugs, the concentrations found for NAX, AMX, IBU and SAL in human urine samples are in accordance with the usual excreted amounts according to the literature data.

Although urine samples containing HIP, ANT, KTP and NIC were not available for the analysis, LOQ values of the proposed EME method are much lower than the usual values for these compounds in human urine samples. According to the literature, levels of approximately 5 mg L^{-1} for ANT, 160 mg L^{-1} for KTP and 300-500 mg L^{-1} for HIP and NIC have been found in human urine samples [32-35]. Therefore, it can be assessed that the proposed EME method could be applied for determining these analytes in real urine samples.

4. Conclusions

Polymer inclusion membranes of 10 μm thickness have been successfully used as support for electromembrane extraction. The composition of PIMs was 29% (w/w) of cellulose triacetate as base polymer and 71% (w/w) of Aliquat®336 as cationic carrier. NSAIDs and highly polar acidic drugs were simultaneously extracted, obtaining recoveries ranging between 81% and 34%. The application of the proposed EME procedure has been assessed for determining the target analytes in human urine samples, thus, PIMs seem to be a good alternative to traditional flat supports for EME.

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Table 1

Table 1. Calibration data, Limits of Detection (LOD) and Quantitation (LOQ) and recoveries for the target analytes in human urine

Analyte	Linear range ($\mu g\ L^{-1}$)	Linearity		LOD* ($\mu g\ L^{-1}$)	LOQ* ($\mu g\ L^{-1}$)	Recovery (%)
		(%)	(R^2)			
NIC	96-500	97.0	0.995	29.0	96.0	81
AMX	333-500	96.9	0.993	100.0	333.0	52
HIP	71-500	97.8	0.997	21.0	71.0	78
ANT	207-500	97.1	0.997	62.0	207.0	34
SAL	61-500	98.0	0.998	18.0	61.0	50
KTP	131-500	96.0	0.993	39.0	131.0	35
NAX	124-500	96.6	0.998	37.0	124.0	48
IBU	62-500	97.7	0.998	19.0	62.0	37

*LOD and LOQ according to the effective recoveries.

Table 2

Table 2. Application of EME proposed procedure to real human urine samples

Analyte	Ingested doses (mg)	Excretion time	Concentration in urine* (mg L^{-1})
AMX	750	7	165
IBU	600	7	259
NAX	550	3	319
SAL	500**	4	711

*RSD < 7%

**As acetylsalicylic acid

Figure 1

Figure 1. Schematic illustration of the experimental device for EME procedure.

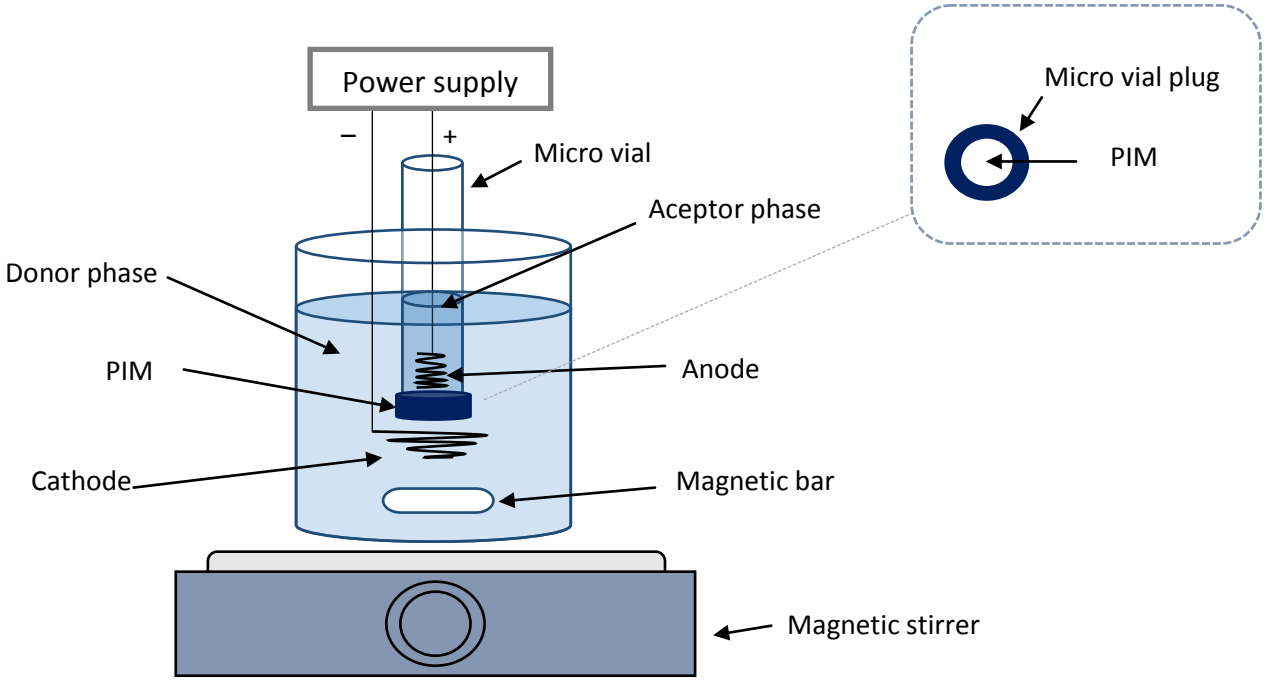


Figure 2

Figure 2. SEM image of a section of the thinner PIM

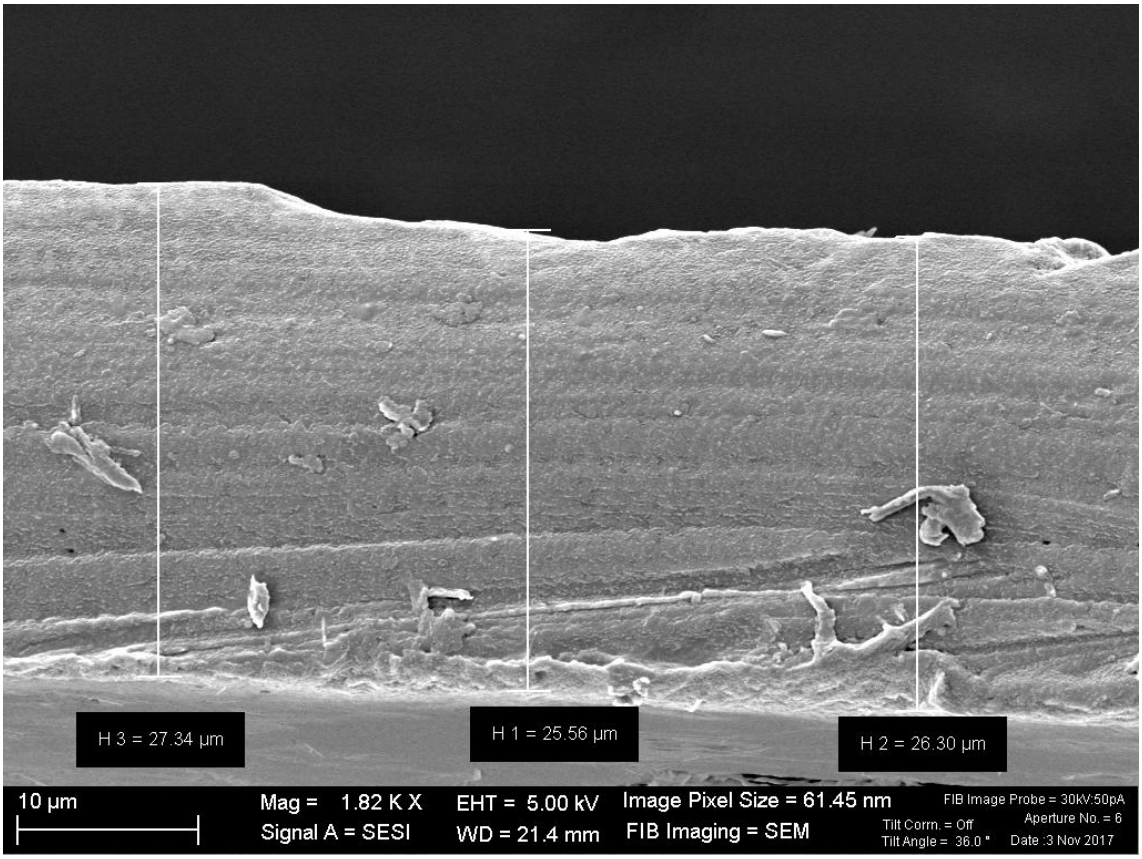


Figure 3

Figure 3. Influence of the acceptor phase pH.

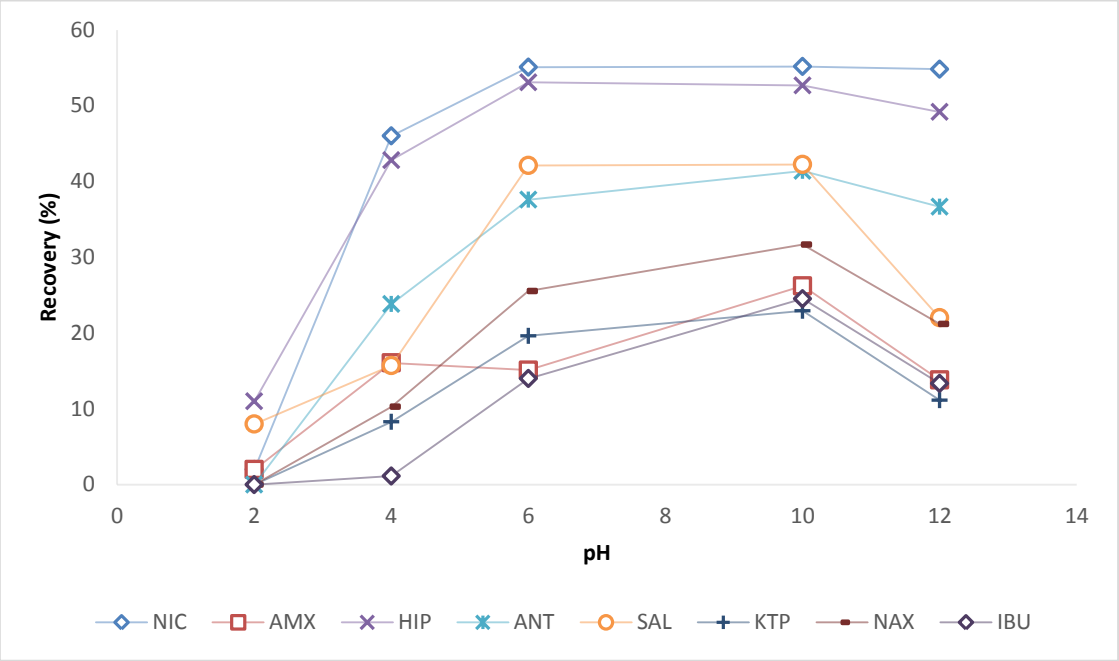


Figure 4

Figure 4. Influence of the applied voltage.

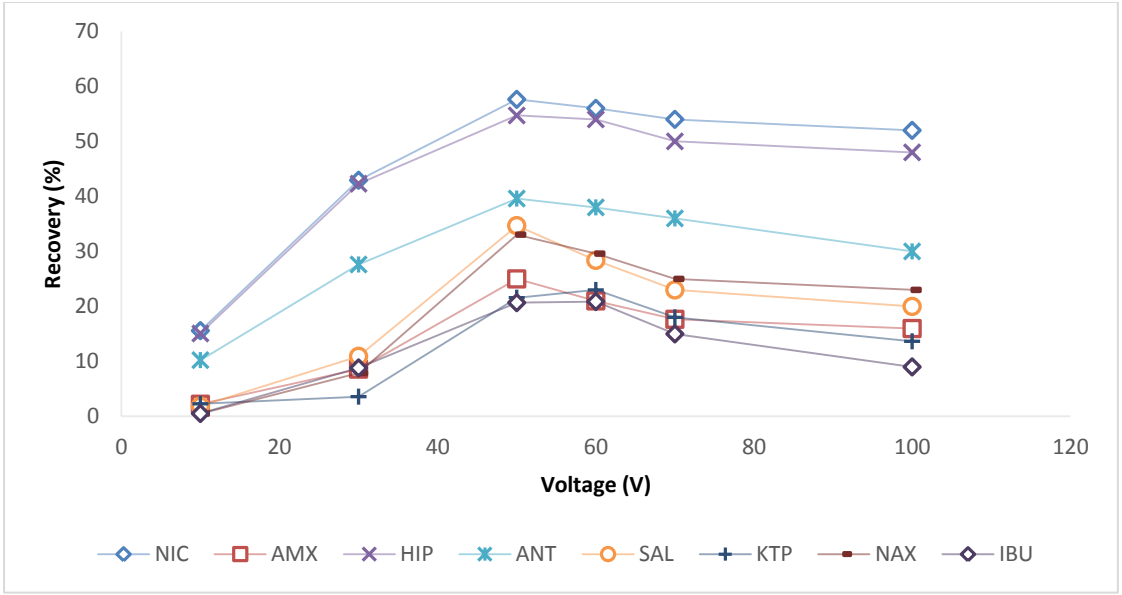


Figure 5

Figure 5. Influence of time of extraction.

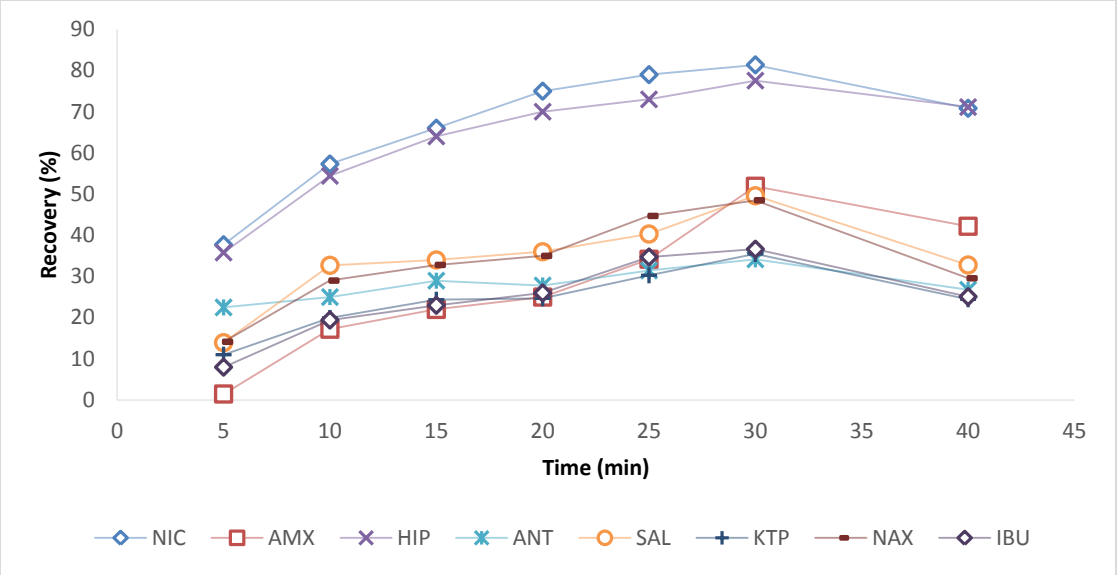
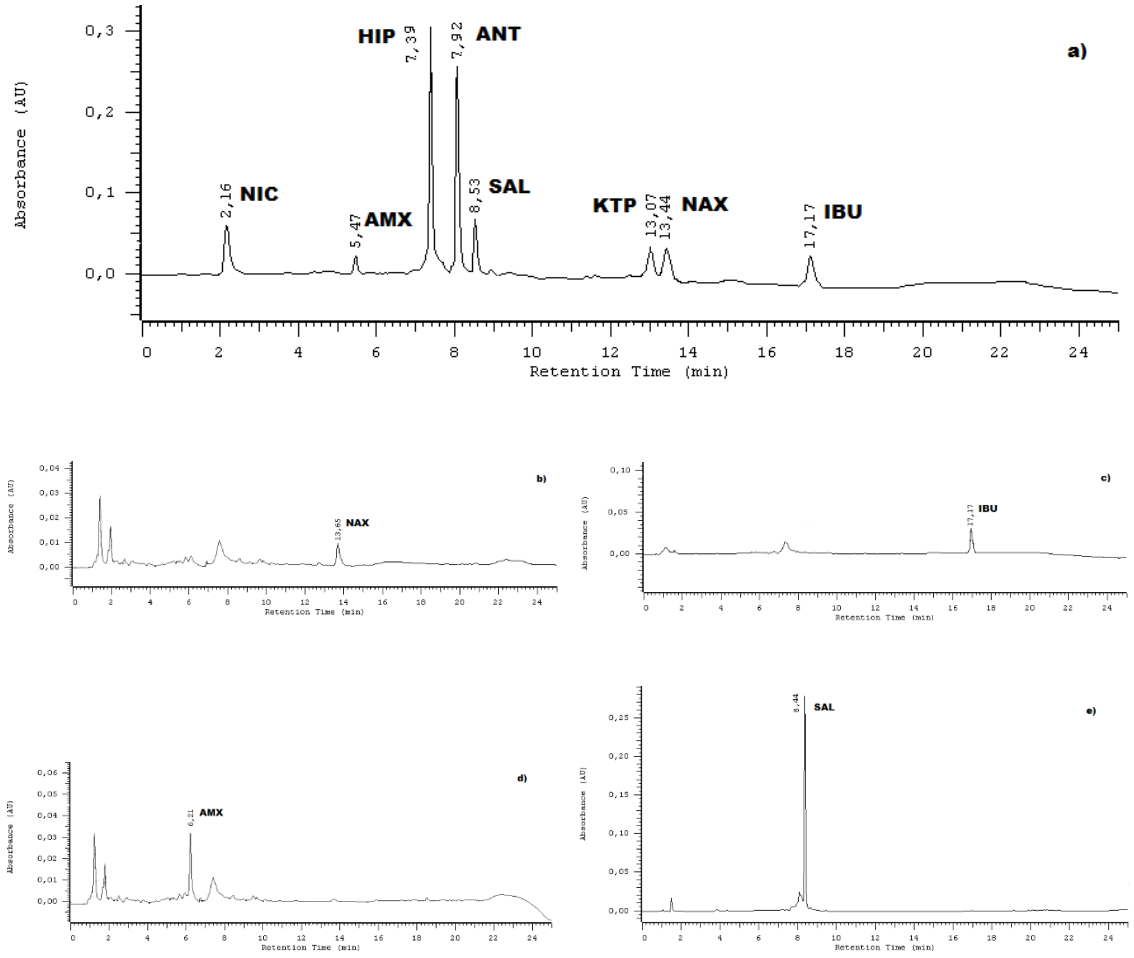


Figure 6

Figure 6. HPLC chromatograms of human urine samples submitted to the EME procedure. (a) human urine sample spiked at 500 µg L^{-1}; (b) human urine sample collected 3h after an oral administration of 550 mg of naproxen; (c) human urine sample collected 7h after an oral administration of 600 mg of ibuprofen (d) human urine sample collected 7h after an oral administration of 750 mg of amoxicillin (e) human urine sample collected 4h after an oral administration of 500 mg of acetylsalicylic acid.



Caption of Figures

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Captions of tables

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***Graphical Abstract (for review)**