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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 25 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.

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

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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 (25 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 300 V 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 Fig. 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 min, maintaining this rate 1 min, then the rate decrease to 60% in 0.1 min, maintaining it for 12 min. Finally, %B (v/v) increases till 100% in 7 min. 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.