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A new effective on chip electromembrane extraction coupled with high performance liquid chromatography for enhancement of extraction efficiency

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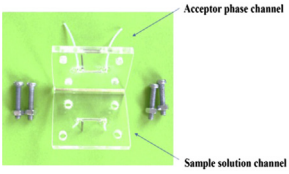
HIGHLIGHTS

- An effective on chip electromembrane extraction (CEME) was designed.
- CEME was coupled with high performance liquid chromatography.
- The method was applied for analysis of nortriptyline and amitriptyline in urine samples.
- Efficient parameters on CEME of the model analytes were optimized.
- The preconcentration factors higher than 17.0-fold and RSDs% < 6.8% were obtained.

GRAPHICAL ABSTRACT



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ABSTRACT

In the present research, an effective on chip electromembrane extraction (CEME) coupled with high performance liquid chromatography was presented for analysis of nortriptyline (NOR) and amitriptyline (AMI) as basic model analytes from urine samples. The chip consists of two polymethyl methacrylate (PMMA) parts with two craved microfluidic channels in each part. These channels were used as flow path for the sample solution and a thin compartment for the acceptor phase. A porous polypropylene sheet membrane impregnated with an organic solvent was placed between two parts of chip device to separate the channels. Two platinum electrodes were mounted at the bottom of these channels that were connected to a power supply providing the electrical driving force for migration of ionized analytes from sample solution through the porous sheet membrane into the acceptor phase. This new setup provides effective and reproducible extractions with low volume of sample solution. Efficient parameters on CEME of the model analytes were optimized using one variable at a time method. Under the optimized conditions, the calibration curve was linear in the range of 10.0–500 μg L^{-1} with coefficient of determination (r^2) more than 0.9902. The relative standard deviations (RSDs %) for extraction and determination of the analytes were less than 6.8% based on six replicate measurements. LODs less than 4.0 μg L^{-1} were obtained for both of the model analytes. The preconcentration factors higher than 17.0-fold were obtained. The results demonstrated that CEME would be used efficiently for extraction and determination of AMI and NOR from urine samples.

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1. Introduction

For several decades, liquid–liquid extraction (LLE) has been utilized for sample preparation prior to analysis by high performance liquid chromatography, and gas chromatography in the field of analytical chemistry [1–4]. In recent years, many efforts have been carried out to miniaturize LLE to micro-fluidic chip devices so this issue has been converted to an important direction in extraction process. Miniaturized devices integrate sample preparation, separation, and detection on a small chip and provide construction possibility of a portable LLE device, rapid analysis as well as reduction of the required amounts of sample solution, organic solvent and chemical reagents [5–7].

In recent years, several LLE micro-fluidic chip systems such as membrane based on chip LLE, in which a porous membrane separates acceptor and donor phases, have been reported [8–11]. In all cases, extraction of target analytes is controlled by passive diffusion. Application of electrical driving force is the current state-of-the-art which presents new possibilities for active extraction, simplifying and shortening the sample preparation process as well as enhancing its extraction efficiency and selectivity [12].

Electromembrane extraction (EME) is an important type of miniaturized electrochemically modulated membrane based LLE technique which was initially suggested by Pedersen-Bjergaard and Rasmussen in 2006 [13]. In this technique, a piece of porous hollow fiber is used as the support that is impregnated with a water–immiscible organic solvent. Two platinum electrodes are placed into the sample solution and acceptor phase, connected to a power supply to provide an electrical field through the membrane. The extraction mechanism of EME is based on electrokinetic migration of ionized analytes through the porous membrane. Compared to passive diffusion, electrokinetic migration appears to be a much more efficient transport mechanism, providing high analyte recoveries in a short period of time [14–20].

Since EME has been introduced to now, noticeable developments have been presented in this technique to improve its applicability more and more [21–27]. In 2010, for the first time Petersen et al. presented a downscaled EME in a microfluidic chip for sample preparation [28]. In this study, sample solution delivered as a micro-flow into the chip system, and basic analytes were extracted into a stagnant acceptor solution [28]. Afterward, several reports have been emerged on implementation of EME as chip based devices to make more developments in this field of area [21,29]. Regarding the chip based sample preparation methods which have been explained in the literature, it can be concluded that miniaturization of extraction techniques is one of the more attractive challenge nowdays with a clear landscape in the future as well as enormous revolution which is predictable in the field of analytical chemistry.

In this research, a new and effective on chip EME setup was introduced for extraction and determination of two basic model analytes from urine samples in which anode and cathode electrodes embedded at the bottom of microfluidic extraction channels. The main effective parameter in EME is the electrical field applied between two electrodes which is a function of the applied voltage and the distance between electrodes [12]. The electrical field is increased by decreasing the distance between electrodes, thus it can be expected that a same electrical field can be achieved for the chip based devices at lower voltages than conventional EME setups due to very close distance between electrodes. This advantage makes possible the construction of portable chip based devices for sample preparation because the required electrical field can be provided by common batteries. On the other hand, unlike the previous studies that electrical field has been applied in a narrow length of the microfluidic channels, in this new chip based device the electrical field is applied along with the whole length of the channels. Therefore, a more efficient electrical field is achieved between the flow path of sample solution and acceptor phase channel in this chip based device which can improve the extraction efficiency, and reduce the needed applied potential for extraction providing more ease toward construction of portable sample preparation systems.

2. Experimental

2.1. Chemicals and reagents

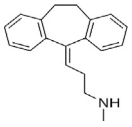
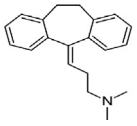
AMI and NOR were kindly donated by Razi Pharmaceutical Co (Tehran, Iran). The chemical structures and physicochemical properties of the drugs are provided in Table 1. 2-nitrophenyl octyl ether (NPOE), tris-(2-ethylhexyl) phosphate (TEHP), and di-(2-ethylhexyl) phosphate (DEHP) were purchased from Fluka (Buchs, Switzerland). 1-Octanol and 1-undecanol were obtained from Merck (Darmstadt, Germany). All chemicals used were of analytical reagent grade. Porous polypropylene sheet membranes with porosity of 55%, wall thickness of 200 μm and pore size of 0.2 μm were purchased from Membrana (Wuppertal, Germany). Ultrapure water was prepared by a Younglin 370 series aquaMAX purification instrument (Kyounggi-do, Korea).

A stock solution containing 2.0 mg mL^{-1} of AMI and NOR was prepared in methanol. All of standard solutions were stored at 4 °C protected from light. Working standard solutions were prepared daily by dilution of the stock solutions with ultrapure water.

2.2. Real samples

To plot the calibration curves and to obtain figures of merit, a human urine sample was collected from a 28-year-old healthy adult male volunteer. The sampling procedure was performed according to the guidelines for research ethics. The sample was filtered through a 0.45-μm pore size cellulose acetate filter from Millipore (Madrid, Spain). The filtrate was collected in a glass container which was carefully cleaned with hydrochloric acid and washed with deionized water and stored at 4 °C to prevent bacterial growth and proteolysis. One milliliter of the urine sample was spiked with a mixed standard solution to obtain the desired concentration. Then, proper amount of NaOH solution (0.1 mol L^{-1}) was dropwise added to adjust pH of the solution at 7.00. These samples were subsequently submitted to on chip EME procedure. Further urine samples were obtained from two healthy volunteers (28-year-old and 47-year-old) that one of them (47-year-old) took a single oral dose of nortriptyline (100 mg).

Table 1
Chemical structures, pK_a and log $K_{O/W}$ of the analytes.

Name	Chemical structure	pK_a	Log $K_{O/W}$
Nortriptyline		10.47	4.43
Amitriptyline		9.76	4.81