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Simultaneous extraction of acidic and basic drugs via on-chip electromembrane extraction

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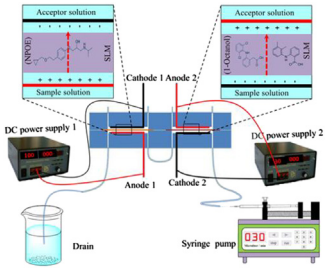
HIGHLIGHTS

- An on-chip electromembrane extraction (CEME) was designed.
- CEME was applied for simultaneous extraction of acidic and basic model analytes.
- All effective variables on extraction efficiency of the model analytes were optimized.
- Calibration curves were linear in the range of 10.0–500 μg L^{-1} with r^2> 0.9982.
- Method requires less volumes of organic solvent, sample and allow easier automation.

GRAPHICAL ABSTRACT



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ABSTRACT

In the present work, a on-chip electromembrane extraction (CEME) was designed and employed for simultaneous extraction of mefenamic acid (MEF) and diclofenac (DIC), as acidic model analytes, and betaxolol (BET), as a basic model analyte, followed by HPLC-UV. The CEME consists of two polymethyl methacrylate (PMMA) parts which each part consists of two separated microfluidic channels. A polypropylene sheet membrane impregnated with an organic solvent was sandwiched between the parts. One of the parts was used as the flow path for the sample solution and the other one as holder for the acceptor phases. The separated microfluidic channels of the sample solution part were connected to each other using a small piece of a capillary tube and the sample solution was pumped through them by means of a micro-syringe pump. However, the acceptor phases of the acidic and basic analytes were separately kept stagnant in the two microfluidic channels during the extraction process. A d.c. potential was applied for migration of the analytes from sample solution through the organic membrane into the acceptor phases. All effective variables on the extraction efficiency of the analytes were optimized. Under the optimized conditions, preconcentration factors higher than 15 were achieved and the calibration curves were linear in the range of 10–500 μg L^{-1} (r^2 > 0.9982). RSD% values (n = 4) and LODs were less than 7.1% and 5.0 μg L^{-1}. The results demonstrated that CEME could efficiently be used for the simultaneous analysis of acidic and basic analytes in biological samples.

1. Introduction

Microfluidic technology has excited the interest of many scientists in different areas especially in the fields of chemical, biological

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and clinical analyses [1–3]. Microfluidic systems are the science of designing, manufacturing, and formulating devices and processes that deal with volumes of fluids on the order of several hundred microliters or lower. Microfluidic systems have diverse and widespread potential applications including blood-cell-separation equipment, biochemical assays, chemical, genetic analysis and sample preparation techniques [2–4].

In the recent years, many efforts have been focused on the design of microfluidic devices in the field of analytical chemistry [1,2,5–9]. The miniaturization of analytical chemistry techniques and devices causes a significant environmental and economical advantage as lower sample, solvent, and reagent volumes consumption.

Over the past decades, liquid–liquid extraction (LLE) has been utilized for extraction and concentration of different analytes as well as elimination of matrix interferences in analytical processes [10–13]. The conventional method of LLE suffers from some drawbacks such as high extraction duration, consumption of large amount of toxic solvents and sample solution and high cost. In order to eliminate these problems, microfluidic systems for LLE have been developed for a wide range of applications, including the separation and purification of various biological and environmental compounds [4,14–17]. Miniaturization of LLE and its combination with microfluidic systems to reduce consumption of toxic organic solvents and sample solutions has led to the development of microfluidic on-chip liquid phase microextraction. Apart from mentioned advantages, the microfluidic on-chip LLE systems may provide higher extraction efficiencies due to increasing the interfacial area and small diffusional lengths [18–20].

In 2006, Pedersen-Bjergaard et al. introduced a novel microextraction technique called electromembrane extraction (EME), as one of the liquid phase microextraction (LPME) approaches [21]. Several different microfluidic EME setups have been introduced, which were able to consider only a single class of analytes (basic or acidic) as a target [22–29]. However, the simultaneous extraction and determination of acidic and basic analytes from a sample solution is a challenging task in chemical analysis when sampling and sample extraction are the limiting factors of the analytical procedure [30–37].

Basheer et al. introduced an interesting EME setup for simultaneous extraction of acidic and basic drugs, in which four sheets of porous polypropylene membrane were heat-sealed at three edges [38]. Two platinum electrodes were inserted in each side of membrane pockets and an electrical potential applied between them. The acidic and basic analytes were first extracted into the aqueous phases filled into the side membrane pockets based on electrokinetic migration and then transferred into an organic acceptor phase filled into the middle membrane pocket. The transport mechanism for the analytes into the organic acceptor phase was passive diffusion and the flux was basically controlled by distribution ratios. Finally, the organic acceptor phase was analyzed by gas chromatography followed by mass spectrometry detection. Yamini et al. introduced a simple and different setup for simultaneous extraction of acidic and basic analytes [39]. In this setup, two pieces of hollow fiber were used which each piece was connected to a needle tip. A platinum electrode was inserted in the lumen of each hollow fiber and an electrical potential was applied between them. The acidic and basic analytes were separately extracted into the lumen of the hollow fibers based on their charges and the charges of the electrodes. Also, Fakhari et al., utilized this setup followed by CE for simultaneous determination of acidic and basic drugs from biological samples [34].

The aim of the current research is to develop a rapid, selective and sensitive EME setup based on microfluidic systems for simultaneous extraction and preconcentration of acidic and basic analytes. A new on-chip EME setup is introduced which in, the anode and cathode electrodes embedded at the bottom of each microfluidic channel. The acidic and basic compounds were extracted toward the channels containing the anode and cathode electrodes, respectively. The key parameter in this microfluidic EME setup is the strength and direction of the applied electrical field, which is a function of the applied voltage and the distance between the electrodes [40]. Mefenamic acid, diclofenac and betaxolol were utilized as the model analytes since the extraction behaviors of these analytes were previously investigated [39,41]. Ultimately, the designed on-chip electromembrane extraction (CEME) was used for analysis of the model drugs in biological samples under the optimal extraction conditions.

2. Experimental

2.1. Chemicals and reagents

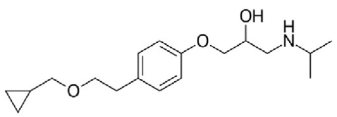
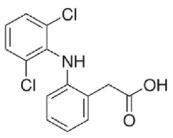
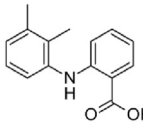
Mefenamic acid (MEF) and diclofenac (DIC) were obtained from the Department of Medical Sciences of Tehran University (Tehran, Iran). Betaxolol (BET) was kindly denoted by Sina Darou (Tehran, Iran). The chemical structures and physicochemical properties of the drugs are provided in Table 1. 2-Nitrophenyl octyl ether (NPOE), tris-(2-ethylhexyl) phosphate (TEHP), and di-(2-ethylhexyl) phosphate (DEHP) were obtained from Fluka (Buchs, Switzerland). 1-Octanol and 1-undecanol were obtained from Merck (Darmstadt, Germany). All chemicals used were of analytical reagent grade. HPLC-grade acetonitrile and methanol were purchased from Caledon (Ontario, Canada). 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).

Stock solutions containing 2.0 mg mL^{-1} of BET, DIC and MEF were prepared in methanol. The standard solutions were stored at 4 °C protected from light. Working standard solutions were daily prepared by dilution of the stock solutions with ultrapure water.

2.2. Real samples

Matrix-matched calibration was used to calculate the concentrations of the target analytes in the real samples. For this purpose, analyte-free urine and plasma samples were spiked with different concentrations of the target analytes and were extracted by the CEME system. The resulted signals for each analyte in each sample were plotted versus the corresponding spiked concentrations and the achieved equations were used as the calibration curves.

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

Name	Chemical structure	pK_a	Log $K_{O/W}$
Betaxolol		9.67	2.54
Diclofenac		4.00	4.26
Mefenamic acid		3.89	5.40