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Application of electromembrane extraction followed by corona discharge ion mobility spectrometry analysis as a fast and sensitive technique for determination of tricyclic antidepressants in urine samples

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ABSTRACT

In the paper, electromembrane extraction (EME) method coupled with corona discharge ion mobility spectrometry (CD-IMS) was introduced for determination of antidepressant drugs (desipramine, sertraline, clomipramine, citalopram) in urine samples. IMS is a well-known, comparatively inexpensive, robust and easy to operate analytical instrumentation. This combination would provide a selective and sensitive determination. In order to achieve the best extraction efficiency, optimization of the variables affecting these methods was carried out. Optimal extractions were accomplished with 2-nitrophenyl octyl ether as the supported liquid membrane, with 190 V as the driving force, and with pH 4 in donor and pH 1 in acceptor solutions. Extractions were obtained after 30 min of operation with the whole assembly agitated at 1000 rpm.

Under the optimized conditions, the proposed technique provided good linearity (>0.9974), repeatability (RSD < 4.5%), low limits of detection (0.9–1.5 ng mL^{-1}), excellent preconcentration factor (PF = 158–190) and high recoveries (79–95%). Finally, developed method was applied to quantification of antidepressant drugs in urine samples.

1. Introduction

Sample preparation is an essential step in the analytical procedure [1]. It is necessary to note that therapeutic level of antidepressants in urine samples is within the range of 100 to 300 ng mL^{-1} and its concentration in urine depends on the prescribed dosage. This concentration range is below the detection limit of most analytical instruments. Besides, direct analysis of biological samples is not possible due to the presence of interfering compounds along with the desired molecule. Therefore, biological samples, such as human plasma and urine, often need a pre-treatment in terms of analyte enrichment, clean-up and matrix separation [2]. During the last decade, many studies have been focusing on the development of environmentally friendly, simple, economical and miniaturized sample preparation methods.

Among these methods microextraction techniques based on supported liquid membrane (SLM) such as liquid-phase microextraction (LPME) [3,4] and electromembrane extraction(EME) [5,6] have attracted significant attention due to its favorable features, e.g. reduced organic solvents consumption, fast pretreatment processing, low volumes of pretreated samples and reasonable analysis costs in recent years. The extraction mechanism hinges on the analyte partitioning between the sample (donor) solution and the extractant (acceptor) solution. In this technique, the porous hollow fiber containing the SLM prevents the migration of salts, biological macromolecules and hydrophilic compounds which provides a very clean acceptor solution [7]. In addition hollow fibers are discarded after each extraction to avoid carry-over from one sample to another. The extraction process in EME is forced by an applied potential difference across the SLM. Charged analytes in the donor solution migrate across the SLM, toward the electrode of opposite charge in the acceptor solution. For the analyte to migrate, it has to be ionic in both acceptor and donor solutions. Besides, EME has been applied for the extraction of heavy metals [8], peptides [9], nerve agent degradation products [10], basic pharmaceuticals [6], enantiomers [11] and acidic compounds [12]. To increase sensitivity and applicability of method toward the determination of antidepressant drugs, EME extraction technique was coupled with ion mobility spectrometry (IMS) detection system.

IMS has been developed as a powerful instrumental technique for qualitative and quantitative analysis of the analytes such as toxic compounds [13], biochemical markers [14], and drugs [15], explosives [16], narcotics [17], herbicides [18], and pesticides [19]. Its main advantages include low detection limit, fast response, simplicity, portability, and relatively low cost. In addition, not only is IMS a simple detector but also it can be used to separate compounds based on their mass,

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charge state and shape. Among the various atmospheric pressure ionization sources used in IMS, corona discharge (CD) has proved to be a good ionization source in IMS and is currently applied in quantifying many analytes [13]. The main advantages of the CD ionization source are simplicity and increased signal-to-noise ratio, which result in a higher sensitivity and a longer dynamic range [20]. This modification may be used to remove background interferences or enhance sensitivity of response.

The combination of extraction techniques with IMS would provide a selective and sensitive determination. The CD-IMS has been combined with different sample preparation methods such as SPME [21,22] and MIP-SPE [20]. In the present report, we have developed an IMS analysis method with corona discharge ionization source (CD) combined with EME system for the simultaneous determination of four widely used antidepressant drugs including desipramine, sertraline, clomipramine, and citalopram in urine samples. This method can present high enrichment factors as well as short analysis time, low detection limit, simplicity, portability and relatively low cost. To the best of our knowledge, EME has never been directly combined with CD-IMS detection.

2. Experimental

2.1. Chemicals and materials

Desipramine, clomipramine, citalopram and sertraline (purity > 99.0%) were obtained from Tofigh Daru pharmaceutical company (Tehran, Iran) and were used without any further purification. Analytical grade KOH and HCl were purchased from Merck (Darmstadt, Germany). 1-hexanol, 1-heptanol, 1-octanol, 1-nonanol, 2-ethylhexanol, nitrobenzene, n-hexane and 2-nitrophenyl octyl ether (NPOE) were from Fluka (Buchs, Switzerland). HPLC grade water was obtained through a Milli-Q® system (Millipore, Milford, MA, USA) and was used to prepare all solutions.

2.2. Standard solutions and biological matrices

Stock solutions of each drug were prepared as 1000 mg L^{-1} in methanol and stored at 4.0 °C protected from light. Then, the required working standard solutions were freshly prepared by appropriate dilution of the stock solutions with 0.1 mM HCl solution.

Urine samples were collected from Taleghani Hospital (Tehran, Iran). The samples were stored at −4.0 °C, thawed and shaken before extraction.

2.3. Calculation of extraction recovery and enrichment factor

The extraction recovery (ER %) of the EME procedure was calculated according to the following equation:

$$ER = \frac{n_{a,final}}{n_{s,initial}} 100\% = \left(\frac{V_a}{V_s}\right)\left(\frac{C_{a,final}}{C_{s,initial}}\right) \times 100\% \quad (1)$$

where $n_{s,initial}$ and $n_{a,final}$ are the number of moles of analyte originally present in the sample and the number of moles of analyte finally collected in the acceptor solution, respectively. V_a is the volume of the acceptor solution, V_s is the volume of sample solution, $C_{a,final}$ is the final concentration of analyte in the acceptor solution, and $C_{s,initial}$ is the initial analyte concentration in the sample solution. The preconcentration factor (PF) of EME procedure was calculated according to the following equation:

$$PF = \frac{C_{a,final}}{C_{s,initial}} \quad (2)$$

2.4. Ion mobility spectrometer

Ion mobility spectrometer (model 1000) that was constructed at Isfahan University of Technology. The main parts of the instrument are consisted of the IMS cell, the needle for producing the corona, two high voltage power supplies, a pulse generator, an analog to digital converter and a computer. Corona discharge ionization source operated in positive ionization mode was used in these experiments. The drift length was 16 cm and an electric field of 500 V cm^{-1} was used. The shutter grid was made of two series of parallel wires biased to a potential, creating an orthogonal field relative to the drift field, to block ion passage to the drift tube. The grid potential is removed for a short period of time by the pulse generator to admit an ion pulse to the drift region. Generally, this period of time was selected 300 s. The IMS cell was housed in a thermostatic oven in which temperature was controlled within ±1 °C. The drift and carrier gas were both, nitrogen and passed through a 13× molecular sieves (Fluka) trap to remove water vapor and other possible contaminations before entering into the IMS cell. All IMS spectra were recorded by Pico scope software to data storage, processing.

The optimized experimental conditions for obtaining the ion mobility spectra of the compounds are listed in Table 1. The injection port temperature was optimized by evaluating the signal intensity for 10 ppm of each drug at different temperatures. The optimized injection temperature varies with the structure of the compound, its stability, and its melting point. In the case of drugs, when temperature increases, the signal intensity increases. The highest possible temperature (i.e. 260 °C) was chosen for the injection port.

Similarly, the best temperature for the IMS cell was found to be the highest available value, i.e. 200 °C. This is high enough to prevent solvent condensation inside the cell. It also helps dehydration of ions, resulting in a better resolution [23]. At lower temperatures, the memory effect was a real challenge. In addition, the high temperature of the cell prevented long memory effects. In this work, the flow of carrier gas 500 mL min^{-1} and flow of drift gas 800 mL min^{-1} was used. The drugs were separated with good resolution.

2.5. Equipment for electromembrane extraction (EME)

The DC power supply used was a PV-300 model (Mobtaker Aryaei J, Zanjan, Iran) with programmable voltage in the range of 0–300 V, providing currents in the range of 0–1 mA. Platinum wires (diameter 0.2 mm) were used as electrodes with an inter-electrode distance of 5 mm in the sample and acceptor solutions. The electrodes were connected to the power supply which resulted in an electrical field of 10 V cm^{-1}. The porous hollow fiber used for the immobilization of the SLM and housing the acceptor solution was a PP Q3/2 polypropylene hollow fiber (Membrana, Wuppertal, Germany) with an internal diameter of 600 μm, wall thickness of 200 μm, and 0.2 μm pores. It was cut into 6.0 cm segments, cleaned in acetone and dried prior to use. During the extraction, the EME cell was stirred with a stirring rate in the range of 100–1250 rpm by a heater-magnetic stirrer model 301 from Heidolph (Kelheim, Germany) using 5 × 2 mm magnetic bars.

Table 1
The optimized experimental conditions for drugs determination.

Parameter	Setting
Length of drift tube (cm)	16
Drift field (V cm^{-1})	500
Corona voltage (V)	3300
Flow of drift gas (N_2, mL min^{-1})	800
Flow of carrier gas (N_2, mL min^{-1})[a]	500
IMS cell temperature (°C)	170–190
Injection port temperature(oC)	260
Pressure (torr)	630
Typical shutter grid pulse width (μs)	100