Polyaniline immobilized on polycaprolactam nanofibers as a sorbent in electrochemically controlled solid-phase microextraction coupled with HPLC for the determination of angiotensin II receptor antagonists in human blood plasma

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Abstract
In this research, electrospun polycaprolactam nanofibers were collected on a fine stainless steel mesh sheet without a binder, and a layer of conductive polyaniline was chemically deposited on the nanofibers. The polyaniline immobilized on the polycaprolactam nanofibers provided high electrical conductivity, acceptable mechanical stability, and a large surface area. This assembly was then used as a working electrode in electrochemically controlled solid-phase microextraction (EC-SPME), a fast and environmentally friendly method. The polymer layers were characterized by SEM and FTIR techniques. Significant factors affecting the EC-SPME efficiency were investigated, including the desorption conditions, the sorbent used, the pH of the sample solution, the extraction voltage, the extraction time, and the ionic strength. Under the optimum conditions, the limits of detection and quantification for the target analytes were 0.9–1.8 μg L⁻¹ and 3.0–6.1 μg L⁻¹, respectively. The linear dynamic range was 5–2000 μg L⁻¹, with R² > 0.993. The method was coupled with HPLC analysis and applied to the determination of angiotensin II receptor antagonists (ARA-II) in human plasma, and relative recoveries of 91.1–104.3% with RSDs of ≤8.3% were obtained.

Keywords Electrochemically controlled solid-phase extraction · Electrosprinning · Polycaprolactam/polyaniline nanofibers · Angiotensin II receptor antagonists

Introduction
Angiotensin II receptors antagonists (ARA-II)s are effective drugs when used to treat hypertension and heart failure [1–3]. ARA-IIs are recommended as the first-line treatment for high blood pressure in the World Health Organization (WHO) guidelines [4]. After oral administration, the maximum ARA-II concentration in plasma is achieved in 0.5–4 h because they are rapidly adsorbed [5]. Several analytical techniques, such as high-performance liquid chromatography–mass spectrometry (HPLC-MS) [6], HPLC–fluorescence detection [7], and UV–vis spectrophotometry [8], have been used to detect ARA-IIs. Due to the low ARA-II concentration in human blood plasma after oral administration, sample cleanup and enrichment procedures need to be applied before attempting to analyze ARA-IIs in plasma [5]. Several extraction techniques, such as in-tube solid-phase microextraction [5], liquid–liquid extraction (LLE) [9–11], solid-phase extraction (SPE) [12–14], and magnetic solid-phase extraction [15], have been applied in the clean-up process and for the preconcentration of these drugs.

Among these extraction methods, SPE provides fast phase separation, a high enrichment factor, low organic solvent consumption, and the flexibility to couple this technique with different detection systems [16]. Electrochemically controlled solid-phase microextraction (EC-SPME) is a combination of electrochemistry and SPE in which a conductive polymer used as an electroactive sorbent is coated onto a working electrode. Among the various types of sorbents employed, conducting
polymers have a range of useful properties, such as hydrophobicity, the ability to engage in π–π and hydrogen-bond interactions, polar functional groups, ion-exchange properties, and electroactivity. In addition, an electric field is applied to the electrode to assist in the extraction of the target analytes. The charge on the conductive polymer can be controlled electrochemically by oxidation or reduction. This leads to the migration of counterions into and from the conducting polymer as the polymer attempts to retain its electroneutrality. The mechanism for the electroextraction achieved with this technique is based on an electrochemical redox transition of the conducting polymer. Thus, EC-SPME offers advantages such as high recoveries and analyte partition coefficients over traditional SPE techniques for polar, aromatic, and charged species [17, 18]. Moreover, it can be performed more rapidly than traditional SPE because of the fast migration of the analytes under the influence of the applied electrical field [17].

Polyaniline (PANI) is a very useful conductive polymer owing to its ease of polymerization, high electrical conductivity, interesting redox properties, and good environmental stability. In addition, it can interact with various compounds via π–π stacking and hydrogen bonding [19]. Thus, PANI is a promising extraction phase in the field of separation science [20]. However, PANI films are generally delicate and fragile due to their weak mechanical and thermal characteristics [21]. In addition, it has a relatively low surface area because it is a linear polymer without any crosslinking [20]. In order to enhance the stability and surface area of PANI, aniline monomers have been polymerized in situ on electrospun polycaprolactam nanofibers. These electrospun polymer nanofibers have received considerable attention due to their large surface area, their applicability in nonwoven fabrics with high porosity, and their high mechanical stability [22]. Polycaprolactam, with its excellent electrospinnability, a large surface area, good mechanical properties, and high flexibility [23, 24], is an interesting polymer for fabricating nanofibers that could be used as a support in the polymerization of PANI.

In the work reported in the present paper, a stainless steel mesh sheet (0.8 cm × 1 cm) was coated with electrospun polycaprolactam (PCL) nanofibers. Aniline monomers were then chemically polymerized on the surfaces of the PCL nanofibers. Polyaniline immobilized on polycaprolactam nanofibers (PCL/PANI), which presented high electrical conductivity, acceptable mechanical stability, and a considerable surface area, was then used as a working electrode in the electroextraction of ARA-IIIs from human blood plasma. To the best of our knowledge, this is the first time that such an assembly has been used for this purpose. The fast migration of the analytes under the influence of the applied electrical field and the low volume of organic solvent employed were found to result in a fast, effective, and environmentally friendly method.

### Materials and methods

#### Chemicals and reagents

Valsartan, losartan, and irbesartan (see Fig. S1 in the “Electronic supplementary material,” ESM) were purchased from the pharmaceutical manufacturers Abidi and Dorsa Darou (Tehran, Iran). Acetic acid, sodium acetate, sodium chloride, hydrochloric acid, ammonium peroxodisulfate (APS), and aniline were obtained from Merck Chemicals (Darmstadt, Germany). Aniline was distilled before use. Formic acid was supplied by Riedel-de Haën (Seelze, Germany). Polycaprolactam (PCL) was provided by Kolon Industries Inc. (Seoul, Korea). HPLC-grade methanol (MeOH) and acetonitrile (ACN) were obtained from Samchun Chemicals (Seoul, Korea). Standard stock solutions of valsartan, losartan, and irbesartan (1000 mg L$^{-1}$) were prepared in MeOH and stored in a refrigerator at 4 °C before use.

#### Instrumentation

HPLC analyses were performed using a CXTH LC3000 chromatograph system (Beijing, China) coupled with a multil wavelength UV3000 UV-Vis detector. The analytical column was a Spherisorb reverse-phase C18 ODS (25 cm × 4.6 mm i.d.); particle size 5 μm. Sodium acetate buffer (solvent A; C = 0.02 m, pH 4.0) and ACN:MeOH (solvent B; 50:50 v/v) were used as the HPLC mobile phase at a flow rate of 0.5 ml min$^{-1}$. Gradient elution was set as follows: 0–10 min, 30% A; 10–30 min, 50% A; 30–40 min 70% A. The wavelength was set at 250 nm.

The morphology of the fabricated adsorbent was characterized using a scanning electron microscope (SEM; Zeiss DSM-960, Oberkochen, Germany). The IR spectra were obtained using a Bruker Equinox 55 FTIR spectrometer (Bremen, Germany). The electrospinning setup consisted of a direct-current high-voltage (0–25 kV) power supply and an SP100HHP syringe for pumping the polymer solution (Fanavar Nano-Meghyas, Tehran, Iran). A commercially available EM state 1 PalmSense (Utrecht, Netherlands) potentiostat was used to apply the potential in the EC-SPME method. The setup used for EC-SPME was a three-electrode system including a stainless steel mesh electrode coated with PCL/PANI nanofibers as the working electrode, a Pt (platinum) counter electrode, and a graphite reference electrode.

#### Real sample pretreatment

A drug-free plasma sample from a healthy volunteer was obtained from the Iranian Blood Transfusion Organization (Tehran, Iran) and stored at −20 °C until use. For the removal of proteins, a 1-mL plasma sample spiked with 200 μg L$^{-1}$ of
each ARA-II was added to 2 mL MeOH [1]. This mixture was sonicated for 1 min and then centrifuged at 6000 rpm for 7 min. Then 4 mL of phosphate buffer (pH ~7, 0.1 M) solution were added to the 1 mL of filtrated supernatant to adjust the pH to 7, and this solution was used for the extraction procedure.

Fabrication of PCL/PANI nanofibers

The PCL nanofibers were produced by an electrospinning technique and deposited on a stainless steel mesh without using a binder. The preparation procedure for the nanofibers can be briefly summarized as follows: 150 mg of PCL were added to 1 mL of formic acid and the mixture was stirred until the PCL had dissolved entirely. Next, 0.5 mL of this solution was loaded into a 2.5 mL syringe, which was then placed in the syringe pump. After that, the electrospinning process was performed for 180 min. The electrospinning conditions were as follows: voltages of +10 kV and −5 kV were applied to the syringe needle and the collector (a 10 × 10 cm² stainless steel mesh), respectively; the distance between the syringe needle tip and the collector was 15 cm; the solution flow rate was 0.5 mL h⁻¹. Aniline and APS were dissolved separately in aqueous 0.35 M HCl to prepare 0.5 M solutions of each for diffusion and polymerization, respectively. The stainless steel mesh coated with electrosprun PCL nanofibers was placed in a petri dish; 5 mL of the aniline/HCl solution were then added to it, and it was maintained at 40 °C for 1 h in a sand bath. After that, it was placed in an ice bath, and 5 mL of the APS/HCl solution were added to it to polymerize aniline at ~5 °C for 1 h. The mechanism for the oxidative polymerization and protonation of aniline with HCl is shown in Fig. S2 in the ESM [25].

To investigate its applicability to EC-SPME, the electrical conductivity of the PCL/PANI coated on the stainless steel mesh (1.53 S m⁻¹) was measured using a RIGOL digital oscilloscope (Beaverton, OR, USA) at a frequency of 50 Hz. The results showed that it could be used as a working electrode in the EC-SPME method.

The procedure

First, 5 mL of the sample solution (200 μg L⁻¹ of each ARA-II) were placed in a vial. Then, a working electrode consisting of 2 mg of PCL/PANI nanofibers coated on a stainless steel mesh (1.2 cm × 0.7 cm), a Pt counter electrode, and a graphite reference electrode were immersed in the sample solution and 0.25 g NaCl were added to it. Next, a constant potential of +0.9 V was applied to the working electrode, and the solution was stirred for 15 min. After that, the working electrode was removed from the solution and immersed in a microtube containing 300 μL of ACN:HCl 99.8:0.2% (the desorption solvent). The microtube was then shaken for 5 min, and 20 μL of the solution containing the desorbed analytes were injected into the HPLC system for analysis. After each extraction, the working electrode was washed with 5 mL of desorption solvent to eliminate any memory effects. A schematic of the synthesis of PCL/PANI nanofibers and the EC-SPME procedure is shown in Fig. 1.

Adsorption mechanism

As mentioned above, and shown in Fig. S2 (see the ESM), during the synthesis of the PANI conductive polymer, high-mobility chloride ions (Cl⁻) were incorporated into the structure of the polymer film. This led to the formation of a conductive anion-exchange polymer. The PANI conductive polymer film permits counterions to move into and from it so that the film maintains its electroneutrality. When an electric field is applied, oppositely charged species in the solution move towards the fibers. These species are concentrated on the fiber surfaces and are replaced in the solution by dopant (chloride ions). If a suitable positive potential is applied to the working electrode, the PANI conductive film is oxidized and the target analytes (the ARA-IIs) in the solution are adsorbed and concentrated on the surface of the electrode [17]. The EC-SPME mechanism for the adsorption of anions is shown in Fig. 2.

Results and discussion

Choice of materials

Due to its highly conjugated structure, polar functional groups, high conductivity, its ability to establish π–π interactions, and its participation in ion exchange processes, PANI has found a broad range of applications in extraction and separation techniques [19] (https://pubchem.ncbi.nlm.nih.gov/compound/). PCL is an interesting material for SPE because of its excellent electrospinnability, large surface area, good mechanical properties, and high flexibility [23, 24]. Thus, in order to enhance the surface area and stability of PANI film, aniline was polymerized in situ on electrospun PCL nanofibers coated onto a stainless steel mesh. The PCL/PANI stainless steel mesh was used as an effective adsorbent working electrode in the EC-SPME method.

Characterization

To prepare PCL/PANI nanofibers, PCL was immersed in an aniline/HCl solution. In this step, hydrogen bonding between the amide groups in PCL and the amino and imino groups in aniline prompted the adsorption of aniline on the surface of the PCL. APS was then added to polymerize the aniline on the surfaces of the PCL nanofibers. Figure 3a and b show SEM images of PCL and PCL/PANI nanofibers, respectively. The smooth and porous surfaces of the PCL fibers before and after
coating them with PANI are clearly shown. The surfaces of the PCL/PANI nanofibers are seen to be porous, demonstrating the formation of a PANI layer on the PCL fibers. As can be seen in Fig. 3c and d (zoomed SEM images of the PCL and PCL/PANI nanofibers), the diameters of the representative PCL and PCL/PANI nanofibers shown are ~148.4 nm and ~216.8 nm, respectively. This indicates that a thin layer of PANI (~34.2 nm) formed on the PCL nanofibers.

Fig. 1 Schematic of the synthesis of polycaprolactam/polyaniline (PCL/PANI) nanofibers and the electrochemically controlled solid-phase microextraction (EC-SPME) procedure

PCL and PCL/PANI nanofibers shown are ~148.4 nm and ~216.8 nm, respectively. This indicates that a thin layer of PANI (~34.2 nm) formed on the PCL nanofibers. Histograms of the diameters of the PCL and PCL/PANI nanofibers, measured using Image J software (version 1.51, LOCI,

Fig. 2 Schematic depicting the adsorption of valsartan, losartan, and irbesartan (ARA-IIs) anions via an ion exchange process on the surface of the polyanionic conductive polymer film
University of Wisconsin, Madison, WI, USA), are shown in Fig. S3 (see the ESM). As seen in the histograms, the PCL and PCL/PANI nanofibers had average diameters of around 120–180 nm and 190–270 nm, respectively.

Figure 3e and f show the FTIR transmittance spectra of the PCL and PCL/PANI nanofibers. In the spectrum of the PCL (Fig. 3e), the peak at 1640 cm\(^{-1}\) corresponds to the stretching vibrations of C=O, while the bands at 2857 and 1535 cm\(^{-1}\) can be ascribed to CH\(_2\) and NH stretching vibrations, respectively. The spectrum of PCL/PANI presented in Fig. 3f shows a band at 3089 cm\(^{-1}\) which can be ascribed to aromatic C–H stretching vibrations. In addition, a broad peak at 3388 cm\(^{-1}\) can be attributed to O–H stretching vibrations.

Selection of the desorption solvent

In order to select the appropriate desorption solvent, ACN, MeOH, acidic MeOH (MeOH and concentrated HCl, 99.8:0.2%), and acidic ACN (ACN and concentrated HCl, 99.8:0.2%) were tested under the initial extraction conditions (pH 8, extraction voltage 1.2 V, ionic strength (salt) 0%, extraction time 20 min, desorption time 10 min). The resulting
data are displayed in Fig. 4a. As can be seen, the highest efficiency was obtained when using acidic ACN as the desorption solvent.

Effect of the pH

The pH of the aqueous sample solution is a significant factor in EC-SPME because it can affect the chemical structures of the analytes. The influence of the pH in the range 2–9 was investigated. As shown in Fig. 4b, the extraction efficiencies of the ARA-IIs were enhanced by increasing the pH to 7 but then decreased at higher pH values. Considering the pKₐ values of the analytes (valsartan: 3.6; losartan: 5–6; irbesartan: 4.61; https://pubchem.ncbi.nlm.nih.gov/compound/), they are all in anionic form at pH 7.0. However, at pH values higher than 7, hydroxide anions compete with the ARA-IIs in anion exchange processes on the surface of the sorbent, decreasing the extraction yield. Therefore, a pH of 7 was considered the optimum value to use in subsequent experiments.

Effect of the extraction voltage

The influence of the adsorption voltage on the extraction of ARA-IIs was investigated by applying potentials in the range 0–1.2 V. The results shown in Fig. 4c indicate that the extraction efficiencies of the ARA-IIs increased as the extraction voltage was increased from 0 to 0.9 V but then decreased at higher voltages. This decrease was probably due to competition between the ARA-IIs and hydroxide ions for adsorption on the PCL/
PANI surface. Therefore, 0.9 V was selected as the best extraction voltage to achieve the maximum adsorption of ARA-IIIs.

**Effect of the ionic strength**

The effect of ionic strength was investigated by adding various amounts of NaCl in the range 0–30% w/v. As shown in Fig. 4d, the extraction efficiencies of ARA-IIIs rose as the salt concentration was increased to 5% w/v (0.25 g); above that, the efficiencies decreased. The ionic strength can influence analyte solubility via salting-in or salting-out effects, but in some cases it does not have a significant effect. In addition, in electrochemical processes, adding salt can increase solution conductivity [18]. However, in this case, when there was a high concentration of the salt, Cl\(^-\) (from the NaCl) competed with the ARA-IIIs for adsorption at the active sites of PCL/PANI, reducing the extraction efficiency. Therefore, 5% (w/v) was chosen as the optimum amount of salt for further experiments.

**Effects of the adsorption time and desorption time**

The effect of the adsorption time (the amount of time that the adsorbent and the sample solution were in contact) on the efficiency of the method was investigated in the range 5–30 min. A potential of +0.9 V was applied to the working electrode, and the solution was stirred. Figure 4e shows that the efficiency increased with stirring time up to 15 min, but then remained approximately constant. Therefore, 15 min was chosen as the optimum adsorption time. In addition, the influence of the desorption time was studied in the range 1–15 min (Fig. 4f), and 5 min was selected for the elution of ARA-IIIs from PCL/PANI fibers.

**Method validation**

The analytical performance of the developed EC-SPME method was assessed under the optimum conditions (elution solvent: acidic ACN (300 μL), pH 7, extraction voltage 0.9 V, salt 0.25 g, extraction time 15 min, desorption time 5 min). Calibration curves were constructed using 5 mL of the prepared plasma sample spiked with the ARA-IIIs at ten concentration levels in the range 1–3000 μg L\(^{-1}\), and the results are shown in Table 1. The linear dynamic ranges were 5–1000, 10–2000, and 5–1000 μg L\(^{-1}\) (\(R^2 > 0.993\)) for losartan, irbesartan, and valsartan, respectively. The limits of detection, based on \(S/N = 3\), were 1.1 μg L\(^{-1}\) for losartan, 1.8 μg L\(^{-1}\) for irbesartan, and 0.9 μg L\(^{-1}\) for valsartan. The limits of quantification (based on \(S/N = 10\)) were 3.9, 6.1, and 3 μg L\(^{-1}\) for losartan, irbesartan, and valsartan, respectively. The intraday and interday relative standard deviations (RSDs, %), < 7.5% and < 8.1%, respectively, were calculated based on measurements of a standard solution of ARA-IIIs (200 μg L\(^{-1}\)) on five different days, with five replicates examined per day. The extraction recoveries

### Table 1 Analytical figures of merit for the developed EC-SPE/HPLC method for the analysis of ARA-IIIs (losartan, irbesartan, and valsartan)

<table>
<thead>
<tr>
<th>Analyte</th>
<th>LOD (μg L(^{-1}))</th>
<th>LOQ (μg L(^{-1}))</th>
<th>LDR (μg L(^{-1}))</th>
<th>(R^2)</th>
<th>Regression equation</th>
<th>ER (%)</th>
<th>RSD% ((n = 3))</th>
<th>Interday ((n = 9))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan</td>
<td>1.1</td>
<td>3.9</td>
<td>5–1000</td>
<td>0.997</td>
<td>(y = 6.10x + 2.56)</td>
<td>69</td>
<td>7.5</td>
<td>8.1</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>1.8</td>
<td>6.1</td>
<td>10–2000</td>
<td>0.993</td>
<td>(y = 3.96x + 5.22)</td>
<td>61</td>
<td>5.4</td>
<td>6.7</td>
</tr>
<tr>
<td>Valsartan</td>
<td>0.9</td>
<td>3</td>
<td>5–1000</td>
<td>0.994</td>
<td>(y = 7.82x + 13.32)</td>
<td>79</td>
<td>6.9</td>
<td>7.1</td>
</tr>
</tbody>
</table>

\(a\) Limit of detection (μg L\(^{-1}\)) (3S/N). \(b\) Limit of quantitation (μg L\(^{-1}\)) (10S/N). \(c\) Linear dynamic range (μg L\(^{-1}\)). \(d\) Determination coefficient. \(e\) Relative standard deviation (%). \(f\) Extraction recovery (%)

### Table 2 Quantitative results for the determination of ARA-IIIs in human blood plasma samples (unspiked and spiked at 100 and 500 μg L\(^{-1}\)) using the EC-SPE/HPLC method

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Losartan</th>
<th>Irbesartan</th>
<th>Valsartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Added (μg L(^{-1}))</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>Found; mean ± SD (μg L(^{-1}))</td>
<td>102.0 ± 8.5</td>
<td>104.3 ± 7.3</td>
<td>91.1 ± 6.8</td>
</tr>
<tr>
<td>RR (%)</td>
<td>102</td>
<td>99.4</td>
<td>91.1</td>
</tr>
</tbody>
</table>

\(a\) Standard deviation. \(b\) Not detected. \(c\) Relative recovery
(ERs) were calculated using the equation below, and the results were in the range 61–79%.

\[
ER(\%) = \frac{C_{\text{os}}}{C_{\text{aq}}} \times \frac{V_{\text{os}}}{V_{\text{aq}}} \times 100,
\]

where \(C_{\text{os}}\) and \(C_{\text{aq}}\) are the analyte concentration in the final organic solvent and the initial concentration of the analyte in the aqueous phase, respectively; \(V_{\text{aq}}\) is the volume of the aqueous sample and \(V_{\text{os}}\) is the volume of desorption solvent.

**Analysis of real samples**

The developed analytical procedure was successfully applied to the determination of the analytes of interest in a real blood plasma sample obtained from a healthy volunteer. The sample was pretreated according to the “Real sample pretreatment” section, and three aliquots—including one unspiked aliquot and two others spiked at two concentrations of ARA-IIs (100 \(\mu\)g L\(^{-1}\) and 500 \(\mu\)g L\(^{-1}\))—were prepared. These aliquots were then analyzed with the developed procedure. No analyte was detected in the unspiked sample. The relative recoveries for the spiked samples were calculated using the following equation:

\[
RR(\%) = \frac{C_{\text{found}} - C_{\text{real}}}{C_{\text{added}}} \times 100,
\]

where \(C_{\text{found}}\) is the concentration of the analyte in the spiked real sample, \(C_{\text{real}}\) is the concentration of the analyte

![Fig. 5](image) Representative HPLC/UV chromatograms of the ARA-IIs in human plasma samples spiked at (a) 100 \(\mu\)g L\(^{-1}\) and (b) 500 \(\mu\)g L\(^{-1}\) as well as in unspiked human plasma (c). 1 Losartan, 2 irbesartan, 3 valsartan

<table>
<thead>
<tr>
<th>Method</th>
<th>Sample</th>
<th>Analyte(s)</th>
<th>LOD (^{\mu})</th>
<th>LOQ (^{\mu})</th>
<th>LDR (^{\mu})</th>
<th>LOD (^{\mu})</th>
<th>LOQ (^{\mu})</th>
<th>LDR (^{\mu})</th>
<th>R(^2)</th>
<th>RSD (%)</th>
<th>Solvent ((\mu)L)</th>
<th>Extraction time (min)</th>
<th>ER (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPE-HPLC/UV e</td>
<td>Plasma</td>
<td>Losartan, valsartan</td>
<td>0.1 0.10 0.99</td>
<td>&gt;10 100 1000</td>
<td>0.1 0.1 0.99</td>
<td>0.1 0.1 0.99</td>
<td>0.1 0.1 0.99</td>
<td>0.1 0.1 0.99</td>
<td>&gt;0.99</td>
<td>1000</td>
<td>&gt;20 300</td>
<td>20 0.99 5 1.8 3</td>
<td>5 2000 &gt;0.994 &gt;7 0 20</td>
<td>61-79 This work</td>
</tr>
<tr>
<td>SPE-HPLC/FD f</td>
<td>Plasma</td>
<td>Losartan, valsartan</td>
<td>87 85 15 0.09</td>
<td>&gt;10 100 1000</td>
<td>87 85 15 0.09</td>
<td>87 85 15 0.09</td>
<td>87 85 15 0.09</td>
<td>87 85 15 0.09</td>
<td>&gt;0.99</td>
<td>1000</td>
<td>&gt;20 300</td>
<td>20 0.99 5 1.8 3</td>
<td>5 2000 &gt;0.994 &gt;7 0 20</td>
<td>61-79 This work</td>
</tr>
<tr>
<td>In-tube SPME g</td>
<td>Plasma, urine</td>
<td>Losartan, valsartan, irbesartan</td>
<td>0.1 0.1 0.99</td>
<td>&gt;10 100 1000</td>
<td>0.1 0.1 0.99</td>
<td>0.1 0.1 0.99</td>
<td>0.1 0.1 0.99</td>
<td>0.1 0.1 0.99</td>
<td>&gt;0.99</td>
<td>1000</td>
<td>&gt;20 300</td>
<td>20 0.99 5 1.8 3</td>
<td>5 2000 &gt;0.994 &gt;7 0 20</td>
<td>61-79 This work</td>
</tr>
<tr>
<td>SPE-HPLC/MS h</td>
<td>Plasma</td>
<td>Losartan, valsartan, irbesartan</td>
<td>0.1 0.1 0.99</td>
<td>&gt;10 100 1000</td>
<td>0.1 0.1 0.99</td>
<td>0.1 0.1 0.99</td>
<td>0.1 0.1 0.99</td>
<td>0.1 0.1 0.99</td>
<td>&gt;0.99</td>
<td>1000</td>
<td>&gt;20 300</td>
<td>20 0.99 5 1.8 3</td>
<td>5 2000 &gt;0.994 &gt;7 0 20</td>
<td>61-79 This work</td>
</tr>
<tr>
<td>In-tube SPME-i-HPLC/UV i</td>
<td>Plasma, urine</td>
<td>Losartan, valsartan, irbesartan</td>
<td>0.1 0.1 0.99</td>
<td>&gt;10 100 1000</td>
<td>0.1 0.1 0.99</td>
<td>0.1 0.1 0.99</td>
<td>0.1 0.1 0.99</td>
<td>0.1 0.1 0.99</td>
<td>&gt;0.99</td>
<td>1000</td>
<td>&gt;20 300</td>
<td>20 0.99 5 1.8 3</td>
<td>5 2000 &gt;0.994 &gt;7 0 20</td>
<td>61-79 This work</td>
</tr>
<tr>
<td>SPE-HPLC/UV i</td>
<td>Plasma</td>
<td>Losartan, valsartan, irbesartan</td>
<td>0.1 0.1 0.99</td>
<td>&gt;10 100 1000</td>
<td>0.1 0.1 0.99</td>
<td>0.1 0.1 0.99</td>
<td>0.1 0.1 0.99</td>
<td>0.1 0.1 0.99</td>
<td>&gt;0.99</td>
<td>1000</td>
<td>&gt;20 300</td>
<td>20 0.99 5 1.8 3</td>
<td>5 2000 &gt;0.994 &gt;7 0 20</td>
<td>61-79 This work</td>
</tr>
<tr>
<td>SPE-LC-MS/MS i</td>
<td>Plasma</td>
<td>Losartan, valsartan, irbesartan</td>
<td>0.1 0.1 0.99</td>
<td>&gt;10 100 1000</td>
<td>0.1 0.1 0.99</td>
<td>0.1 0.1 0.99</td>
<td>0.1 0.1 0.99</td>
<td>0.1 0.1 0.99</td>
<td>&gt;0.99</td>
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<td>20 0.99 5 1.8 3</td>
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<td>61-79 This work</td>
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<tr>
<td>EC-SPE-HPLC/UV i</td>
<td>Plasma</td>
<td>Losartan, valsartan, irbesartan</td>
<td>0.1 0.1 0.99</td>
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a Limit of detection (\(\mu\)g L\(^{-1}\)). b Limit of quantitation (\(\mu\)g L\(^{-1}\)). c Linear dynamic range (\(\mu\)g L\(^{-1}\)). d Determination coefficient. e High-performance liquid chromatography-diode-array detection. f Magnetic solid-phase extraction.
in the real sample, and $C_{\text{added}}$ is the concentration of standard solution added to the real sample. As reported in Table 2, the recoveries for the spiked samples were in the range 91.1–104.3% (RSD ≤ 8.3%). Representative chromatograms of the ARA-IIs in human blood plasma samples spiked at two concentration levels are shown in Fig. 5.

**Comparison with other methods**

A literature survey indicated that limited research had been published on the determination of angiotensin II receptor antagonists (Table 3). A comparison between relevant published methods and the developed model shows that the proposed method has lower or comparable LODs and RSDs compared with the other techniques. In addition, the extraction time needed for this method is shorter than those of the other methods. This can be ascribed to the fast migration of the analytes under the influence of the electrical field applied to the sorbent. Moreover, the volume of organic solvent consumed in the extraction is lower than in some published methods but comparable to the volumes used in others. The extraction recoveries are comparable with those achieved with other methods. Therefore, the results showed that the proposed method could be used for the analysis of ARA-IIs in human plasma samples.

**Conclusions**

In this work, polycaprolactam nanofibers were electrospun on a stainless steel mesh, and these fibers were coated with polyaniline, which was subsequently doped with high-mobility chloride ions and oxidatively polymerized in situ. The resulting assembly was used as a novel working electrode in electrochemically controlled solid-phase microextraction for the first time. The optimized method was coupled with high-performance liquid chromatography and used for the determination of angiotensin II antagonists in human blood plasma without prior derivatization of the analytes. The polyaniline immobilized on polycaprolactam nanofibers provided good electrical conductivity, acceptable mechanical stability, and a large surface area. This method was found to be fast (an extraction time of 20 min and an analysis time of 35 min) and environmentally friendly (it utilized only 300 μL of organic solvent for analyte desorption). The method was successfully applied to the extraction of angiotensin II receptor antagonists from human plasma, and provided acceptable limits of detection (0.9–1.8 μg L$^{-1}$), linear dynamic ranges (5–2000 μg L$^{-1}$), and good precision (RSD% < 8.1).

**Compliance with ethical standards**

The human blood plasma sample was obtained from a healthy volunteer, with informed consent provided to the Iranian Blood Transfusion Organization (Tehran, Iran).

The studies were performed in accordance with the ethical standards approved by the appropriate research ethics committee of University of Tehran.

**Conflict of interest**

The authors declare that they have no conflicts of interest.

**References**


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