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Research Article

Determination Of Ciprofloxacin In Pharmaceutical Dosage, Human Serum and Urine, Using Molecularly Imprinted Polymer Modified Electrode By Voltammetry

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Abstract

Molecularly imprinted polymer based working electrode was prepared for the determination of ciprofloxacin (CF). Electrochemical behavior of CF was investigated by differential pulse voltammetric (DPV) method in the range of 10-60% (v/v) acetonitrile (MeCN)-H_2O binary mixture at the pH between 3-7 prepared Britton-Robinson (BR) buffers. Voltammetric analyzes were performed with molecularly imprinted (MIP) and non-imprinted (NIP) modified electrodes. The influence of the electropolymerization cycles, solution pH, and MeCN-H_2O ratio, on the performance of both electrodes were evaluated and optimized. Detection limit was obtained as 1.12×10^{-5} M (S/N=3). Recommended method was successfully employed for determination of CF in pharmaceutical, human serum and urine.

Keywords: Ciprofloxacin, Polypyrrole, Biological sample, Differential puls voltammetry, Molecularly imprinting

Farmasötik Dozaj, İnsan Serumu ve İdrarındaki Siprofloksasinin Moleküler Baskılı Polipirol Modifiye Elektrot Kullanılarak Voltametrik Tayini

Öz

Siprofloksasin tayini için moleküler baskılı polimer bazlı çalışma elektrodu hazırlanmıştır. Siprofloksasinin elektrokimyasal davranışı % 10-60 (v/v) asetonitril-su ikili karışımında ve pH 3-7 aralığında hazırlanan Britton-Robinson (BR) tamponu kullanılarak diferansiyel puls voltametrisi (DPV) yöntemiyle incelenmiştir. Voltametrik analizler moleküler baskılı (MIP) ve baskısız (NIP) modifiye elektrotlar ile gerçekleştirilmiştir. Elektropolimerizasyon döngü sayısı, çözelti pH'sı ve asetonitril-su oranının her iki tip elektrodun performansı üzerindeki etkisi araştırılmış ve optimize edilmiştir. Dedeksiyon limiti 1.12×10^{-5} M (S/N = 3) olarak bulunmuştur. Önerilen yöntem farmasötik dozajda, insan kanı ve idrarındaki siprofloksasinin tayini için başarıyla uygulanmıştır.

Anahtar Kelimeler: Siprofloksasin, Polipirol, Biyolojik numune, Diferansiyel puls voltametri, Moleküler baskılama

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1. Introduction

Ciprofloxacin (CF), [1-cycloprophyl-6-fluoro-1,4-dihydro-4-oxo-7-(piperazinyl)quinolone-3-carboxylic acid] (The formula of CF is in Fig.1), a second generation fluoroquinolone, is one of the most important quinolone derivatives in clinical use and has a broad spectrum of activity against Gram negative and Gram positive bacteria [1-3]. Some fluoroquinolones have been developed especially for veterinary practice, such as enrofloxacin (ENRF), while others like CF are limited to human treatment [4]. CF is used in a broad range of urinary, respiratory, gastrointestinal tract infections [5]. However, recently, misuse of antibiotics in food producing animals has caused a wide anxiety among the public because of the transfer of antibiotic-resistant bacteria from animals to human beings. [6]. Numerous methods have been reported for the detection of CF in the literature; such as, high performance liquid chromatography (HPLC) [7-13] using various detectors, liquid chromatography-mass spectrometry (LC/MS) [14], capillary electrophoresis [15], UV spectrophotometry [16], adsorptive stripping voltammetry [17] and electrochemical analysis [18,19]. Among all the above, electrochemical method may be the most widely used due to its advantages of selectivity, sensitivity, quick response and low cost.

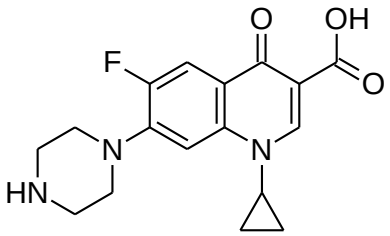


Fig. 1. Chemical structure of ciprofloxacin.

In the new analytical techniques MIPs have gained growing interest as a novel type of sorbent with alluring properties [20]. This interest can be explained by the advantages of the MIPs, like superior stability, low cost and simple preparation. MIPs are prepared in the presence of a target molecule whose functional and cross linking monomers are co-polymerizated in a solution. This procedure can be performed between imprint molecules and monomers by means of either reversible covalent bonding or non-covalent interactions [21]. MIPs have been applied in different kinds of methods, like liquid chromatography [22,23], solid phase extraction [24,25], solid phase micro-extraction [26], capillary electrophoresis [27], and electrochemical sensors [28-31].

Owing to the high affinity, selectivity and mechanical stability, imprinted polymers have been used for the determination of drugs. In this work we developed a sensor based on molecularly imprinted polymer electrodes to make easy and fast detection of ciprofloxacin by voltammetry. MIP and NIP electrodes were prepared by CV and electrochemical behavior and determination of CF were performed by DPV. European Union (EU) Legislation has established the safe Maximum Residue Limits (MRLs) of the veterinary drugs in animal edible tissues. Total maximum residue limit for enrofloxacin and ciprofloxacin is 100 μg/kg. Its successful application to the determination of CF in commercial pharmaceutical sample and biological samples has been demonstrated.

2. Material and Method

2.1. Apparatus

Autolab/PGSTAT 302 N was used for analysis of CF which is controlled by a Nova 2.1.4 software version (Ecochemie, Netherlands). Ag/AgCl (3M) electrode as reference, and a Pt wire as auxiliary electrode, were used. As working elektrot, imprinted and non-imprinted polypyrrole modified pencil graphites were used. Voltammograms were recorded under Nitrogen atmosphere, at room temperature.

2.2. Chemicals

Ciprofloxacin (≥ 98.0%) was obtained from Aldrich, tetra-n-butylammonium tetrafluoro-borate (TBATFB) ≥ 98.0 %, acetic acid (≥ 99.8%), sodium hydroxide (≥ 97%), boric acid (99.5-100.5%), acetonitrile (≥ 99.9%), ortho-phosphoric acid (85%), and pyrrole (≥ 97%), were supplied by Merck. Deionized water (ultra-pure) was used in all solutions. Ciprofloxacin tablets were purchased from a local pharmacy in Turkey.

2.3. Working Electrode Preparation

The interior of a Scrikss tipped pencil was adapted as the holder for the graphite tip. Two types of modified electrodes were prepared using pyrrole for monomer and the simultaneous electropolymerization was performed on the pencil graphite surface. The basic principle of molecular imprinting is based on the process of cross-linked monomers forming copolymerization in the presence of a target analyte that acts as a molecular template.

MIP electrodes were recorded by cyclic voltammetry (CV). CV voltammograms were taken in the range of 10-60 % (v/v) MeCN-H_2O binary mixture, in the presence of 1×10^{-1} M pyrrole [21,28-31], 1×10^{-1} M TBATFB and 1.36×10^{-3} M CF. 100 mV/s was scan rate. NIP electrodes were also obtained under the same conditions to check the dependability of measurements.

2.4. Overoxidation of PPy Films

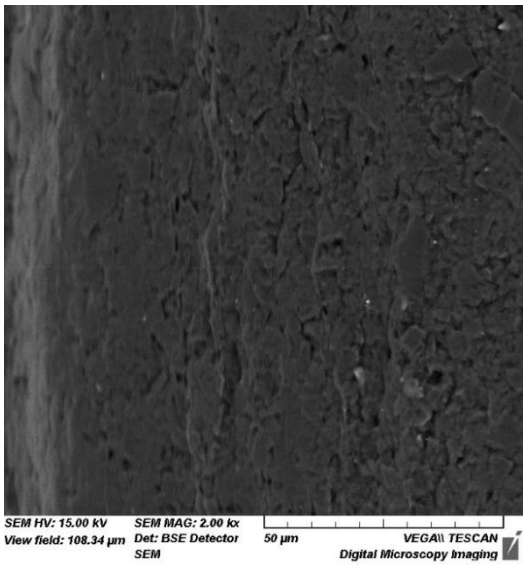
PPy films were overoxidized by CV at the scan rate of 50 mV/s by scanning potential from +0.80 to +1.20 V for twenty times in 1×10^{-1} M NaOH solution [21,28]. In this procedure, by overoxidation, both the PPy was overoxidated and the template molecules was removed from the PPy films.

2.5. Surface Morphologies

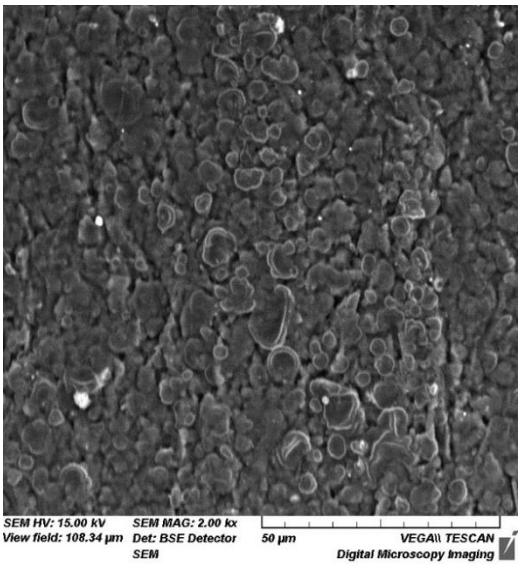
Surface morphologies of pencil graphite electrode (PGE) and MIP film were studied with scanning electron microscopy (SEM) image and shown in Fig.2. As can be seen from the images, the MIP film seems to be more porous structure than the PGE because molecularly imprinting causes rearrangement of polymer chain packing. MIP films are easy to handle, robust, and very compact. The overoxidation procedure greatly influences the surface morphology, that actually give rise to an important difference in anion and cation uptake selectivity.

2.6. Characterization of Ciprofloxacin

Electrochemical characterization of ciprofloxacin was researched by modified electrodes. Catalytic effect of MIP electrode is displayed in Fig.3. Ciprofloxacin gives an oxidation peak response at around 1.25 V.



(a)



(b)

Fig. 2. SEM photographs of (a) NIP and (b) MIP electrode.

The maximum peak current at around 1.25 V for ciprofloxacin at MIP and NIP electrode are, 1.4×10^{-4} A, and 3×10^{-5} A respectively. The obtained current response with NIP electrode, is lower than with the MIP electrode. These values explain that the MIP electrode is more selective and sensitive than the NIP electrode against CF as seen in Fig.3.

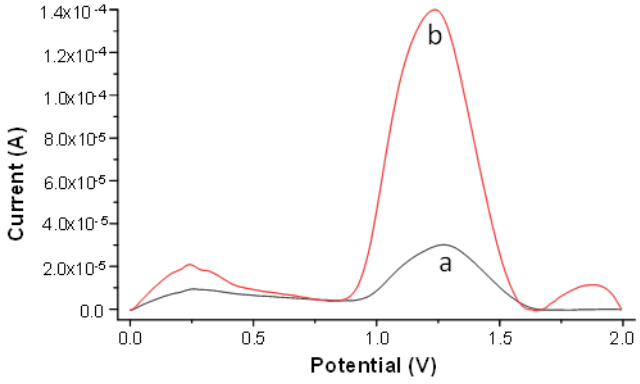


Fig. 3. DP voltamograms for CF at (a) NIP electrode, (b) MIP electrode in 40% (v/v) MeCN–H_2O BR buffer at pH 5.0.

A CF calibration plot was obtained by plotting ΔI versus CF concentration in 40% MeCN–H_2O (v/v) BR buffer at pH 5.0. A linear relation was observed in the range of 5×10^{-5} - 5×10^{-3} M with a correlation coefficient of 9.99×10^{-1}. The detection limit was determined as 1.12×10^{-5} M (S/N=3).

Table 1 shows calibration characteristics and related parameters using MIP electrode for CF. The limit of detection (LOD) and the limit of quantification (LOQ) were calculated for CF with MIP electrode according to the 3 s/m and 10 s/m criterious, respectively.

Table 1. Characteristics of ciprofloxacin plots in 40% (v/v) MeCN-H_2O BR buffer at pH 5.0 using MIP electrode.

	Ciprofloxacin (M)
Linearity Range (M)	5×10^{-5} – 5×10^{-3}
R^2	9.99×10^{-1}
LOD (M)	1.12×10^{-5}
LOQ (M)	3.73×10^{-5}

2.7. Analysis of Ciprofloxacin in Pharmaceutical, Human Serum and Urine Samples

CF containing commercial drug, was analyzed for estimation of CF. The tablets (each tablet contains 500 mg of ciprofloxacin hydrochloride (HCl) equivalent to 500 mg ciprofloxacin) were weighed, powdered and dissolved in 40% (v/v) MeCN-H_2O BR buffer (in a 25 mL volumetric flask) at pH 5.0 [18,19]. The solution was sonicated with ultrasonic stirrer 20 min and filtered through a 0.45 µm nylon syringe filter. Different concentrations of this solution were added to the electrochemical cell and DP voltammograms were recorded.

Serum and urine samples were obtained from healthy individuals before the experiments, were prepared as follows: the blood sample santrifüjed 10 minutes (4000 rpm) and the supernatant was taken and equal volumes of MeCN was added and centrifuged 15 min (12000 rpm) for the protein precipitation. The supernatant was taken and added to the stock solution (prepared with CF) mentioned before, to be 10 percent of total volume, and different concentrations of this solution were added to the electrochemical cell and DP voltammograms were taken. Also, urine samples were prepared with the same procedures as their ratios to be 10%, and analyzed. The same experimental conditions were applied to the NIP electrode. Table 3 demonstrates the gained data when the DPV is used, with MIP electrode.

3. Results and Discussion

MIP and NIP electrodes were prepared by CV deposition of pyrrole in the presence of TBATFB with and without CF on a pencil graphite electrode, respectively.

The experiments were performed using a cell which is composed of three-electrode system, the NIP or MIP electrode as the working electrode, a platinum wire as the auxiliary electrode, and the Ag/AgCl as a reference electrode. This method was also used for determination of CF in commercial pharmaceutical

tablet and biological samples.

3.1. Cyclic Voltammetry

Cyclic voltammograms obtained for MIP and NIP electrodes in the presence of 1×10^{-1} M pyrrole, 1×10^{-1} M TBATFB and in the presence and absence of 1.36×10^{-3} M CF in 10-60% (v/v) MeCN-H_2O binary mixture at the pH between 3-7 prepared BR buffers.

3.2. Differential Pulse Voltammetry

The voltammetric behavior of CF on imprinted and non-imprinted films were investigated by differential pulse voltammetry in BR buffer solutions (working media and BR buffers were mentioned above). In Fig.4 differential pulse voltammograms for solutions containing increasing concentrations between 5×10^{-5}-5×10^{-3} M CF standard at MIP electrode were given. The current of the MIP electrode was found to increase with increasing CF concentration.

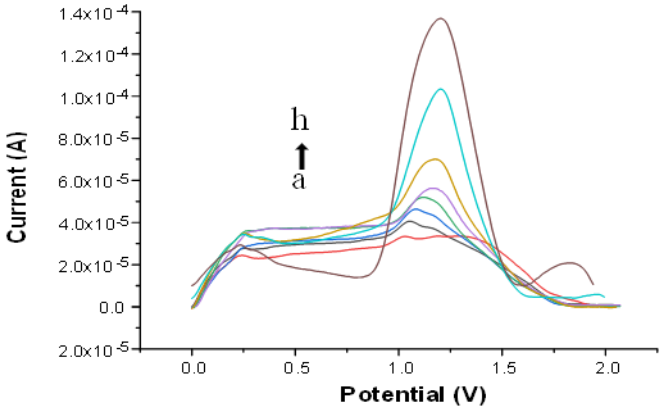


Fig. 4. DP voltammograms of CF at varying concentration in the range of 5×10^{-5}-5×10^{-3} M (a-h) at the MIP electrode in 40% (v/v) MeCN-H_2O BR buffer at pH 5.0.

3.3. Influence of MeCN-H_2O Ratio

The influence of MeCN-H_2O ratio of solution on the MIP electrodes was investigated by DPV in the range of 10-60% (v/v) MeCN-H_2O binary mixture (increasing by 10 units) at the pH between 3-7 prepared Britton-Robinson (BR) buffers. The reproducibility, repeatability and the highest peak current intensity were obtained in 40% (v/v) MeCN-H_2O BR buffer at pH 5.0. Therefore, 40% (v/v) MeCN-H_2O BR buffer at pH 5.0 was selected for optimum working media (the data were not given here).

3.4. Influence of pH

The influence of pH on the electrochemical oxidation of CF at the MIP electrode was investigated by the DPV in the range of 3-7. The voltammetric response of CF is sorely affected by pH. Well defined peaks were obtained at pH 5.0, as seen from the Fig.5 oxidation currents decreased below and above pH 5.0. This pH is in agreement with Nawaz and Kawde's studies in the literature [18,19].

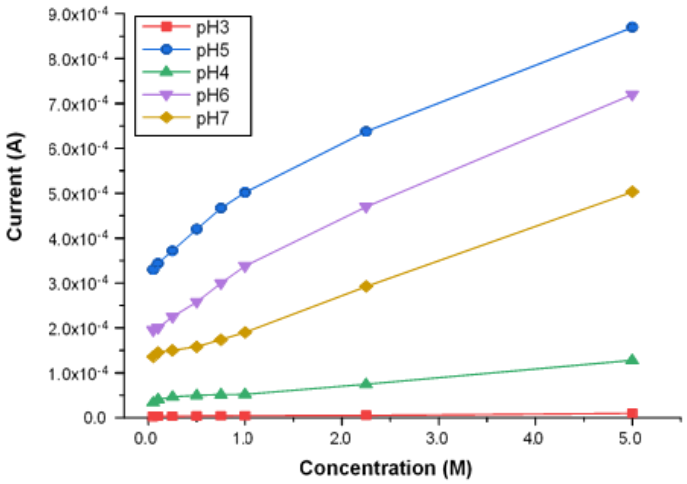


Fig. 5. The influence of pH on the peak current of CF at MIP electrode in 40% (v/v) MeCN-H_2O BR buffer.

3.5. Influence of the Electropolymerization Cycles

The optimum CV cycles for the formation of the 'sensing' layer of MIPs were detected from a series of experiments. These electrodes were prepared with different number of cycles at controlled potential from −0.6 V to +1.4 V reducing the potential value 0.1 V, in different ratio of MeCN–H_2O (v/v) binary mixture solution of 1×10^{-1} M TBATFB, 1.36×10^{-3} M CF and 1×10^{-1} M pyrrole. The MIP electrode was prepared at between 3 to 7 cycles for the control of polymer thickness. The highest current difference between the MIP and NIP electrodes for CF was obtained by applying five cycles in the electropolymerization. So, the number of optimum polymerization cycles was chosen to be five cycles.

3.6. Influence of Interferent

The determination of CF in the presence of ofloxacin (OFL) under the same experimental conditions was studied with MIP electrode. The oxidation currents in varying concentration of OFL at a fixed concentration of CF were analyzed by DPV. The obtained current in the absence of interferent was 3.4×10^{-5} A. The results are given in Table 2. That is, the modified MIP electrode can recognize the CF molecules by means of shape selection and the size of functional groups.

Table 2. Influence of interferent (Ofloxacin), at the MIP electrode, on the DPV response.

Concentration of interferent (M)	Change in current response (A)[a]
2.5×10^{-4}	1.2×10^{-6}
5.0×10^{-4}	1.8×10^{-6}
7.5×10^{-4}	2.1×10^{-6}
1.5×10^{-3}	3.5×10^{-6}

[a]The current in the absence of any interferent was 3.4×10^{-5} A.

3.6. Electrochemical Determination of Ciprofloxacin in Pharmaceutical and Biological Samples

Purposed method is used for determination of CF in pharmaceutical, human serum and urine, in order to confirm the reliability of the overoxidized polypyrrole electrode as a sensor. For the detection of CF in pharmaceutical tablets and biological samples DPV technique was used. The solutions obtained by dissolution of ciprofloxacin tablets were diluted so that ciprofloxacin concentration lies in the range of calibration plot. Differential pulse voltammograms were then recorded under exact identical conditions that were employed while recording differential pulse voltammograms for plotting calibration plot. Fig. 6, 7 and 8 shows DP voltammograms of drug, urine and serum at MIP electrode, respectively. Reported and experimentally detected ciprofloxacin amount in tablets, and spiked and determined amounts in serum and urine are listed in Table 3. In this table we can observe that this detection method was useful for analytical applications.

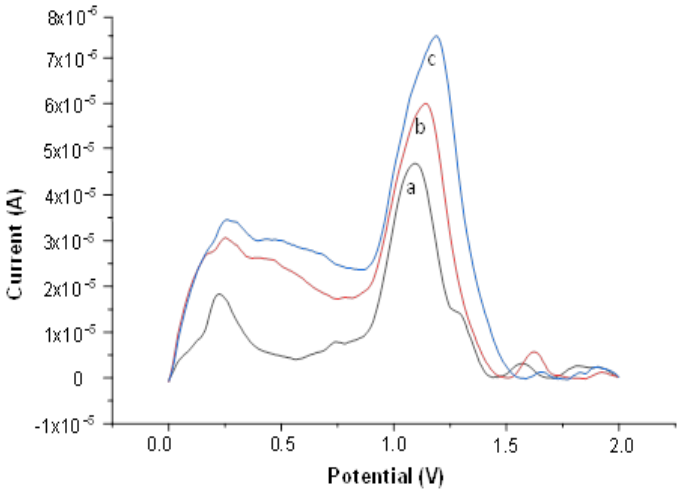


Fig. 6. DP voltammograms, at MIP electrode, for (a) $9x10^{-4}$ M, (b) $1.5x10^{-3}$ M and (c) $2.5x10^{-3}$ M CF, in drug.

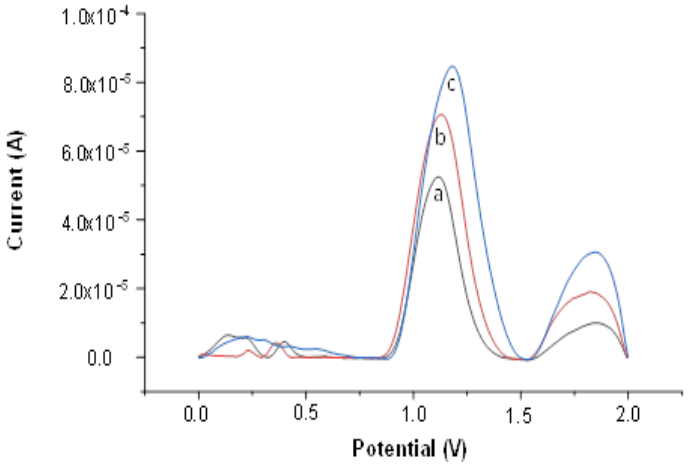


Fig. 7. DP voltammograms at MIP electrode, for (a) $9x10^{-4}$ M, (b) $1.5x10^{-3}$ M and (c) $2.5x10^{-3}$ M CF, in urine.

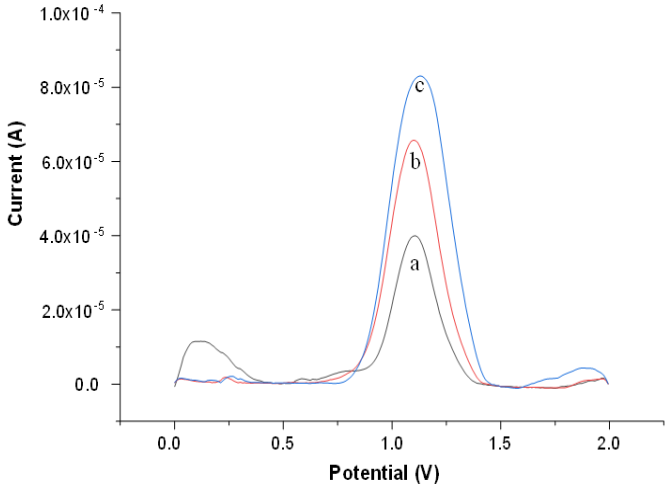


Fig. 8. DP voltammograms at MIP electrode, for (a) $9x10^{-4}$ M, (b) $1.5x10^{-3}$ M and (c) $2.5x10^{-3}$ M CF, in serum.

Table 3. Results of determination and recovery analysis of ciprofloxacin in pharmaceutical and biological media.

	Pharmaceutical	Urine	Serum
Reported content	500[a]		
Spiked ciprofloxacin (M)	$2.50x10^{-3}$	$2.50x10^{-3}$	$2.50x10^{-3}$
Detected ciprofloxacin (M) with MIP	$2.43x10^{-3}$	$2.55x10^{-3}$	$2.65x10^{-3}$
RSD,%	0.48	0.63	0.52
Recovery (%)	97.4	104.4	101.8

[a] mg/capsule.

4. Conclusions and Recommendations

In our work, ciprofloxacin imprinted and non-imprinted modified electrodes has been prepared by the cyclic voltammetric deposition of polypyrrole film on the pencil graphite surface. To investigate electrochemical behavior and determination of CF, modified electrodes were used. The response of NIP and MIP electrodes was compared and observed that the MIP electrode showed high selectivity and sensitivity toward ciprofloxacin. The highest anodic current of ciprofloxacin that was yielded in BR buffer solution was prepared in 40% (v/v) MeCN-H_2O at pH 5.0. This fabricated electrode has been successfully applied as a sensor for easy, simple, fast and sensitive detection of ciprofloxacin in pharmaceutical and biological samples. The PPy modified electrodes are disposable simple to construct, have a good mechanical stability and low response time. The proposed method could find application for the detection of ciprofloxacin level in clinical and pharmaceutical samples.

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