RESEARCH ARTICLE

Multi-template molecularly imprinted polymer hybrid nanoparticles for selective analysis of nonsteroidal anti-inflammatory drugs and analgesics in biological and pharmaceutical samples

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Abstract

The multi-template molecularly imprinted polymers reinforced with hybrid oxide nanoparticles were developed for the selective separation and determination of the trace level of naproxen (NPX), methocarbamol (MTH), and omeprazole (OMZ) simultaneously from biological and pharmaceutical samples. The polymers were constructed by magnetic core@shell molecularly imprinted polymer nanocomposite (Fe_3O_4/ZnO/CuO/MWCNT@MIP). An electrochemical sensor has been fabricated for this purpose. Fe_3O_4/ZnO/CuO/MWCNT nanocomposite was introduced to improve the electron transport capability and increase the sensor surface area, as well as enhance the electronic conductivity. The triple-template MIP-coated layer provides simultaneous selective identification of three analytes by using $[Fe(CN)_6]^{3-/4-}$ as the redox probe. Electrochemical behavior of MTH, NPX, and OMZ on the modified electrode (Fe_3O_4/ZnO/CuO/MWCNT@MIP) by various techniques such as cyclic voltammetry, differential pulse voltammetry, and chronoamperometry was examined. The morphology of the modified and unmodified carbon paste electrodes was performed by scanning electron microscopy (SEM) and X-ray diffraction analysis (XRD). The average crystal size for fabricated nanoparticles obtained by calculating the X-ray diffraction technique was 17 nm in the Scherer method. The particle size which was determined by SEM was 48 nm. Some electrochemical parameters such as the diffusion coefficient and electron transfer coefficient were determined. The effect of many variables such as the pH and scan rate was also investigated. Under optimal conditions, the sensor is designed in the linear range 5.0 nM-100 μM and 5.0 nM-100 μM and 1.0 nM-130 μM with a detection limit of 1.5 nM, 1.0 nM, and 0.7 nM for measurement OMZ, NPX, and MTH, respectively. The relative standard deviation (RSD) of the five measurements was 1.21%, 2.23%, and 2.56% for NPX, MTH, and OMZ. Finally, the designed sensor was successfully used for simultaneous detection of target analytes in the real samples; tablets, water samples, and biological samples.

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Introduction

The use of drugs to treat various types of diseases is indispensable in today's advanced world. Due to different types of diseases, and the prevalence of new diseases due to environmental pollution, the drugs used have also changed (Khan et al. 2020a, b, c). Due to the large amount and different varieties of drugs that are sold without a prescription in pharmacies, it is difficult to control its use. As a result, domestic and hospital wastewater that is contaminated with drug waste pollute the environment and it endangers the whole ecosystem (Khan et al. 2020a, 2020b). Today, the measurement of drugs in pharmaceutical and biological samples along with

medical science has helped to improve a variety of diseases (Qu et al. 2013; Khan et al. 2020a, b, c; Khan et al. 2020b).

Naproxen [(+)-2-(6-metoxy-2naphthyl) propionic acid] is a nonsteroidal drug and is widely used in the treatment of many diseases such as rheumatoid arthritis, joint disease, acute gout, and early painful menstruation (Zhu and Ju 2004). Several methods reported for the determination of naproxen in bio-fluids, such as high-temperature phosphorimetry (Asadi et al. 2015), liquid chromatography (Sadecka et al. 2001), and capillary electrophoresis (Beitollahi and Yoonesfar 2016). A review of the articles shows that naproxen is electrochemically active, so electrochemical methods have been used to measure it (Tashkhourian et al. 2014; Carpenter 1958). Due to the slow oxidation kinetics, and low sensitivity of naproxen measurements using electrochemical methods, the selection of a suitable catalyst to improve the analytical parameters has always been important.

Methocarbamol [2-hydroxy-3-(2-methoxyphenoxy) propyl carbamate)] is a widely used muscle relaxant drug used to relieve acute muscle and bone pain (over a short period time) (Ghoneim and El-Desoky 2010). It is usually presented in the drug formulation alone or combination with another active ingredient. Methocarbamol is mainly excreted by the kidneys (Weng et al. 1994). Several methods were reported for the determination of naproxen, such as spectroscopy (Sane et al. 1987), gas chromatography (Patil et al. 1998), supercritical fluid chromatography (Gholivand and Khodadadian 2011), and voltammetry (Tutunji et al. 2007).

Omeprazole (OMZ), (5-methoxy-2 [[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1H benzimidazole) is a benzimidazole drug. By inhibiting the gastric enzyme system, it can effectively control gastric acid production and therefore be used to treat duodenal ulcers, gastric disease (Nevado et al. 2014; Kulkarni and Balkrishna 2012). Several methods have been reported for the determination of omeprazole, such as chromatography (Lotfy et al. 2016), spectrophotometry (Nevado et al. 2005), electrophoresis (Chomisteková et al. 2017), and electrochemistry (Shahrokhian et al. 2015).

Despite the many instrumental methods used to diagnose drugs, it is always worthwhile to find ways to measure them in complex matrices. So, the sample preparation method is crucial in analytical chemistry and particularly for the complicated matrices encountered in environmental and biological samples. Among the sample preparation methods, solid-phase extraction, especially selective adsorbents, is of special importance.

Molecularly imprinted polymers (MIPs) are the synthetic polymer with unique characteristics such as stability in harsh conditions and selective molecular detection due to the presence of recognition sites within the polymer network regarding size, shape, and orientation of the functional groups complements the analyte molecule. MIPs are commonly used in various arenas, mainly in electrochemical sensors due to its special structure and unique properties including specific recognition capability. On the other hand, the presence of MWCNTs in the polymer structure with the high contact surface, good electrical conductivity, and the unique chemical properties can strengthen the adsorbent by creating MWCNTs − MIP nanocomposite on the electrode surface and accelerate the analyte trapping (Akir et al. 2016). Zinc oxide semiconductor (ZnO) due to its good catalytic performance, low cost, high stability, and non-toxicity is known as one of the most effective and environmental-friendly catalysts. But, zinc oxide has a wide gap band (3.2 V) (Akir et al. 2016). Therefore, it is necessary to modify its structural as well as optical properties by connecting ZnO with other short-band semiconductors such as CuO (Mageshwari et al. 2015; Lu et al. 2009). On the other hand, carbon-coated Fe_3O_4 naoparticles demonstrated that Fe_3O_4/C displays higher capacitance. This event arises due to the presence of a carbon layer that makes the particles undamaged and increases the electronic conductivity of the electrode (Afkhami et al. 2016).

Carbon paste electrode be a member of the heterogeneous carbon electrodes which are generally used in voltammetric, potentiometric, and amperometric measurements. Carbon paste electrodes in a simple way and at the lowest price are obtained. These electrodes are simply used to prepare modified electrodes with different modifiers. These types of electrodes are highly selective for organic and inorganic compounds (Gupta et al. 2018).

In this research, we applied several nanoparticles with different properties as the sensor modifier material, Fe_3O_4/ZnO/CuO/MWCNT and the triple-template MIP, to make a modified carbon paste electrode with a satisfactory analytical response toward NPX, MTH, and OMZ detection simultaneously for the first time. The fabricated sensor was characterized by several techniques. The experimental factors and electrochemical oxidation of analytes at the modified electrode surface were investigated in detail by cyclic voltammetry, differential pulse voltammetry, and chronoamprometry. The analytical efficiency of the assembled sensor was assessed by quantitative measurment of target analytes in real sample matrices, and the results proved that the Fe_3O_4/ZnO/CuO/MWCNT@MIP CPE sensor has satisfactory results with respect to other reported sensors.

Experimental

Apparatus

All electrochemical measurements were taken using potentiostat/galvanostat (Sama 500, analyzer system, Iran). Measurements of cyclic voltammetry, differential pulse

voltammetry, chronoamperometry in a three-cell cap electrode with a capacity of 20 ml, consisting of an Ag/AgCl reference electrode containing potassium chloride saturation solution, the auxiliary electrode of the platinum wire, and the modified carbon paste electrode was taken as a working electrode at laboratory temperature (25 ± 0.5 °C). Excel software was used to record voltammograms and calculations. To adjust the pH, a digital pH meter, model 827 with a combined pH electrode was used (Metrohm, Switzerland). The chemicals were weighted by a SCALTEC SBA/SBC Balance (Sartorius, Germany) with an accuracy of 0.0001 g. The morphology and size of nanoparticles and modified carbon paste electrodes were investigated using a scanning electron microscope (SEM, Hitachi S-4160, Japan). The X-ray diffraction (XRD, Philips, the Netherlands) was used to determine the phase type and size of the crystals. To do this, the PW1800 X-ray machine from Philips and a copper lamp were used. The samples used for this experiment were in powder form. Heidolph Elektro GmbH magnetic stirrer (Germany) and Binder-FD vacuum oven (Germany) were used to synthesize nanoparticles. In all experiments, double-deionized water were prepared by Aqua Max-Ultra Youngling water purifier (South Korea, Seoul). The ultrasonic cleaner (KODO, South Korea), model 1200, was used to clean the surface of the electrodes, better disperse the carbon nanoparticles, and prepare homogeneous solutions from the tested samples.

Materials and reagents

All chemical reagents were of analytical grade (≥ 98% purity) and used as received without further purification. Methacrylic acid (MAA, 99.0%), ethylene glycol dimethacrylate (EGDMA, 99.0%), acetonitrile, iron hexachloride ($FeCl_3.6H_2O$, 99.0%), iron tetrachloride ($FeCl_2.4H_2O$, 99.7%), copper sulfate (CuSO4, 99.0%), zinc sulfate (ZnSO4, 99.0%), methanol, N, N dimethylformamide, acetone, ethanol, from Merck (Germany), and hydrochloric acid (37.0%), nitric acid, sulfuric acid, phosphoric acid (85.0%), acetic acid, potassium dihydrogen phosphate, and potassium hydroxide used in the preparation of buffers were purchased from Sigma-Aldrich Company (USA). Naproxen, methocarbamol, and omeprazole were purchased from Pars Darou Company (Iran) with high analytical purity grade. Nitrogen gas with a purity of 99.99% for degassing solutions in cyclic voltammetry and differential pulse voltammetry studies was prepared from the Roham Gas Company of Iran. Multi-walled carbon nanotubes with a purity of 95% with an average outer diameter of 20–30 nm, length of 1–15 μM, and number of walls of 3–15 in this study were prepared from the Iranian Petroleum Industry Research Institute. Phosphate buffer solutions by adding dilute H_3PO_4 and KOH solutions to 0.5 M KH_2PO_4 salt solution (phosphate buffer) and acetate buffer solution by adding dilute KOH solution to 0.5 M acid solution (acetate buffer) and adjusting the pH of the resulting solution were prepared. Stock solutions of naproxen, methocarbamol, and omeprazole (0.001 M) were prepared by dissolving appropriate amounts of them in methanol solvent and refrigerated at 4 °C. Standard aqueous solutions were diluted daily with stock solutions of buffer (support electrolyte) were obtained. Phosphate buffers with different pHs were used. Pre-activation of the modified carbon paste electrode in 0.1 M solution of phosphate buffer solution was performed for 60 s by applying an activation potential of + 1.45 V (relative to the Ag/AgCl reference electrode).

Synthesis of magnetic carbon nanotubes

Multi-walled carbon nanotubes (MWCNTs) prepared by chemical vapor deposition (CVD) were used in this work. To purify carbon nanotubes to remove catalytic impurities and amorphous carbon, they were first heated in a furnace at 400° C for 40 min. Next, to oxidize the purified nanotubes, we first mixed nitric acid and concentrated sulfuric acid in a ratio of 3:1 and reached a volume of 80 ml. 1 g of nanotubes was added to the solution. The mixture was boiled at 80° C for 8 h without stirring by reverse distillation. The sample was cooled to room temperature and added to 200 ml of distilled water. The oxidized nanotubes were separated by centrifugation and washed again with distilled water. Centrifugation and washing continued until the neutral pH was reached. The active nanotubes were then dried in an oven at 100° C and stored in closed containers. To prepare the magnetic nanotubes, 1.49 g of $FeCl_3.6H_2O$ and 0.76 g of $FeCl_2.4H_2O$ were weighed and transferred to a 200-ml beaker containing 150 ml of double-distilled water. Then the dissolution operation was performed in a container under N_2 gas at a temperature of 70° C (Li et al. 2018). After, 0.5 g of oxidized nanotubes was introduced into the container under constant stirring. This operation was performed for 10 min to create a suspension. Then 30 ml of sodium hydroxide with a concentration of 2 mol/l was added dropwise to the sample container until the pH of the solution reached 10.5. Then, for the growth of crystals, the reaction was performed at 70° C for 4 h under stirring with a magnetic stirrer. After these steps, the magnetized nanotubes were collected by a magnet. Then, by spilling the solution into the container, sediment particles were easily separated. Then, to adjust the alkaline effects of sodium hydroxide, the precipitate was washed twice with distilled water several times. Finally, these sediments were dried in an oven at 70° C for 3 h (Xu et al. 2003).

Synthesis of modified magnetic nanocomposites

To synthesize Fe_3O_4/MWCNTs/CuO-ZnO nanocomposite, the stoichiometric ratio (1:1:1) by co-precipitation method with

ultrasonic assistance was used. In this method, 0.0023 mol of oxidized magnetic nanotubes (Fe$_3$O$_4$/MWCNTs-COOH) was dissolved in 30 ml of deionized water under a magnetic stirrer. Then 0.0023 mol of copper sulfate salt (CuSO4. 5H2O) and 0.0023 mol of the sulfate salt (ZnSO$_4$.7H$_2$O) were added to the mixture and subjected to ultrasonic for one hour. Then, one molar solution of sodium hydroxide was added dropwise and slowly stirred until the solution reached a pH of 12. The solution was transferred to a round bottom balloon and exposed to 120° C for 3 h. After cooling the mixture at room temperature, the suspension was collected with a strong magnet and dried in an oven at 60° C for 7 h. Then, the materials were calcined at 300° C for 3 h (Taufik and Saleh 2017). Nanocomposites synthesized by scanning electron microscopy (SEM) and X-ray diffraction (XRD) were characterized and are used for the modified carbon paste electrode.

Preparation of molecularly imprinted polymer

Synthesis of the molecularly imprinted polymer can be done in different ways. In this study, the non-covalent imprinted method was used. Molecularly imprinted polymer in the presence of naproxen, methocarbamol, and omeprazole as target molecules was synthesized using a Soxhlet apparatus (Binder, Germany) as follows:

0.1 g of each drug and 0.33 g of methacrylic acid (MAA) were added to 30 ml of acetonitrile solvent. The solution was sonicated for 10 min and stirred for 2 h. To remove oxygen, N$_2$ gas was passed through the solution for 10 min. Then 3.2 g of ethylene glycol dimethacrylate (EGDMA) (cross-linking monomer) and 20 mg of azobisisobutyronitrile (AIBN) (initiator) were added to the stirring mixture. The mixture was placed in a sealed container at 60° C for 24 h, and polymerization was performed. Then, the mixture was cooled and collected at the bottom of the container. The resulting polymer was then preheated to 100° C for 24 h and dried. The dried polymer is pulverized in a laboratory mortar (Porcelain Mortar) and used in Soxhlet containing acetic acid and ethanol solution in a volume ratio of 1:9, respectively, to extract target molecules from the MIP lattice, non-reactive monomers, and cross-linkers. Then, distilled water was used to wash and remove acetic acid and ethanol. The product was collected and dried at 60° C. Also, the non-imprinted polymer (NIP) was prepared by a similar method in the absence of the target molecule (Rajabi and Zarezadeh 2016).

Method of preparation of unmodified and modified carbon paste electrode with Fe$_3$O$_4$/MWCNTs/ CuO-ZnO/MIP nanocomposite

In this study, carbon paste prepared by mixing graphite powder and paraffin oil with a weight ratio of 25:75%. The mixture was stirred in a mortar for at least 20 min until completely homogeneous. Then the prepared paste was inserted and pressed at the end of a polyethylene pipe with an inner diameter of 3.4 mm and a height of 15 cm. To establish the electric current, a copper wire was placed in the electrode structure. To prepare the modified paste electrode, 0.9 g of graphite powder and 0.045 g of Fe$_3$O$_4$/MWCNTs-CuO-ZnO nanocomposite and 0.18 g of molecular mold polymer were poured into a hand mortar and mixed by grinding for 5 min. Then, drop by drop, paraffin oil was added to it, and after each step, add the ground mixture until a completely uniform modified paste was obtained. The amount of oil added should be such that the resulting paste has a butter-like consistency. After uniformity, the prepared paste was inserted into the end of the tube with a diameter of 3.4 mm, and by rubbing its surface on a sheet of white paper, a completely smooth and uniform surface was obtained. For electrical connection of the electrode, a copper wire was used (Motaharian et al. 2020) (Scheme 1).
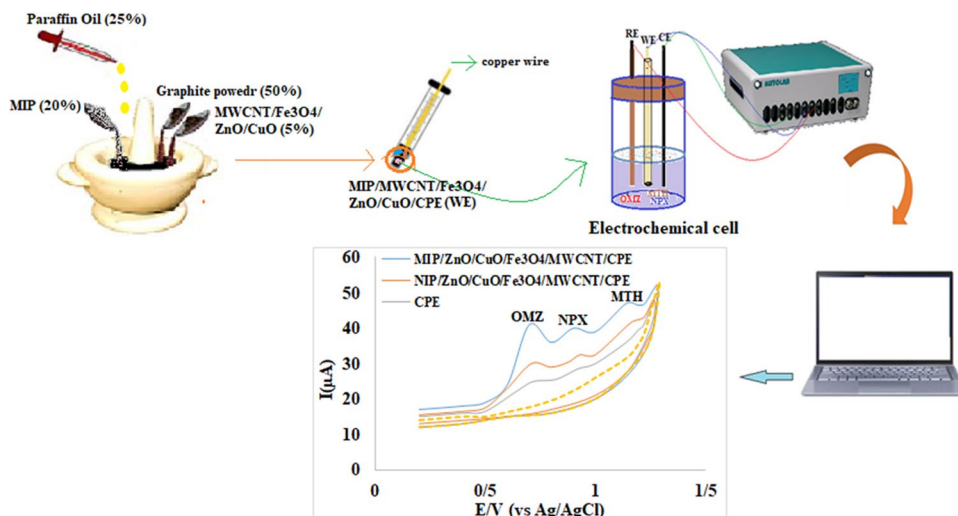
Analytical method

The cyclic voltammetry (CV) technique was used to investigate the initial electrochemical behavior of the three drugs. Differential pulse voltammetry (DPV) was used as an efficient and sensitive method for the development of this electrochemical sensor for simultaneous measurement of drugs in real and biological samples. The experiments were performed in such a way that after preparing the modified electrode, a certain volume was transferred from the standard solution to the electrochemical cell, and the pH of the medium was adjusted by adding a certain amount of electrolyte solution containing 0.4 M potassium chloride at pH = 7; then, the volume of the solution was increased to 10 ml using distilled water twice. After adjusting all the connections of the electrodes, the working solution was deoxygenated by blowing nitrogen gas (99.9% purity), and then, electrochemical measurements were performed (Scheme 1). A pre-potential of -0.5 V was applied to the electrode for 15 s, and then, the voltammogram was scanned in the range of 0.6 to 1.3 V. Application of pre-potential for a suitable time leads to the accumulation of analyte on the surface of the modified electrode and increases the sensitivity of the electrode during electrochemical analysis. Also, the standard addition method was used to determine and measure the species in real samples (Motaharian et al. 2020).

Method of preparing a real sample

The urine samples were stored in the refrigerator after collection. Then, 4 ml of the urine solution was centrifuged (5 min at 1500 rpm) to separate the suspended particles from the urine sample. These particles sometimes

Scheme 1. Construction of a carbon paste sensor modified with MIP/MWCNTs/Fe$_3$O$_4$-CuO-ZnO for simultaneous determination of omeprazole, naproxen, and methocarbamol

Results and Discussion

Morphology and identification of Fe$_3$O$_4$-CuO-ZnO nanoparticles

The analysis of the sample structure by the XRD method is also clearly shown in Fig. 1(a). The lattice fringes correspond to the (311), (110), and (102) planes of the cubic spinel structure of Fe$_3$O$_4$, monoclinic structure of CuO, and hexagonal wurtzite of ZnO, respectively. The average crystal size of the particles with the most intense peak was calculated based on the Scherrer equation:
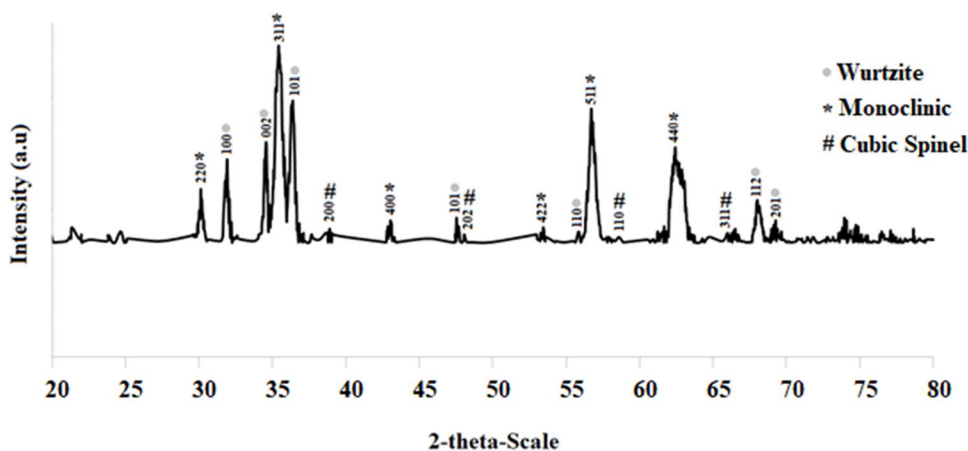
$$D = 0.9\lambda/\beta \cos \theta \tag{1}$$

where D is the average crystalline size, λ is the radiation wavelength X-ray, β is the peak width at half height, and θ is the Bragg angle. The monocrystalline average size was obtained based on Scherer equation of about 17 nm.

Particle size and morphology of the nanoadsorbent samples were identified by SEM. The SEM images in Fig. 1(b) show that the sample contains aggregated particles with a morphology of spherical. The average size of the synthesized nanoparticles was 48 nm.
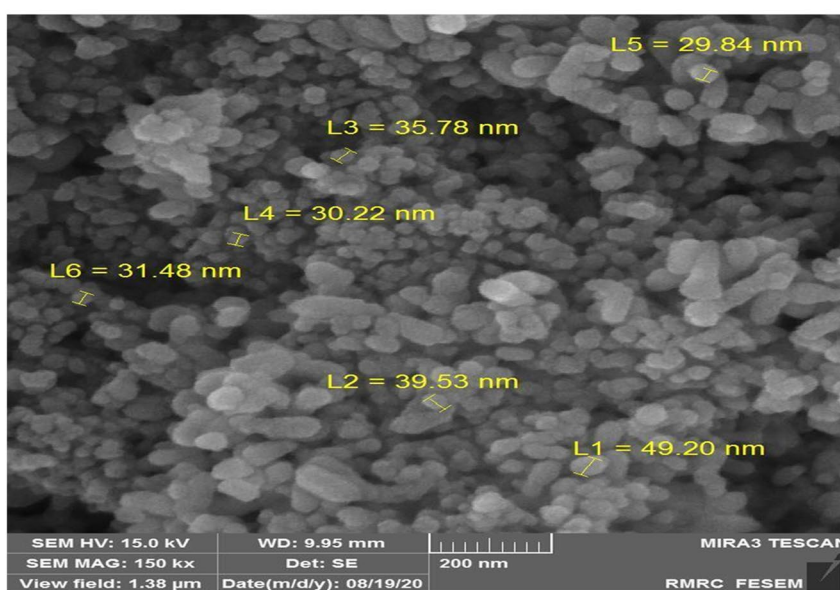
The microscopic study of Fe$_3$O$_4$/ZnO/CuO/MWCNT@MIP nanocomposite

The scanning electron microscopy was used to study the structure of magnetic nanocomposite in carbon paste tissue. The surface of CPE and Fe$_3$O$_4$/ZnO/CuO/MWCNT@MIP nanocomposite was evaluated by SEM technique. Figure 2(a) shows that CPE consists of graphite with a plate morphology (Mbokou et al. 2016). With the addition of

contaminate the surface by adsorption on the electrode and reduce its efficiency. Therefore, the prepared sample was passed through a suitable filter. The upper solution was diluted with the buffer solution. The prepared samples were stored in the refrigerator at 4° C. Water samples were diluted with phosphate buffer (pH = 7) and spiked with different amounts of drugs. The proposed method were used for species analysis (Kyzas et al. 2015).

The plasma samples were stored in a freezer after preparation from a medical diagnostic laboratory in Bojnourd, Iran. Before the analysis, these samples were prepared as follows. The samples were first centrifuged. Then, 4 ml of methanol was added to precipitate the proteins. The precipitated proteins were centrifuged for 2 min at 2000 rpm and separated. The resulting clear solution was transferred to a voltammeter tube after filtration and dilution with phosphate buffer. Then, under optimal conditions, the content of naproxen, methocarbamol, and omeprazole in the sample was calculated by the standard addition method (Kyzas et al. 2015).

To show the efficiency of the method for analyzing drug samples, a sample of tablets was selected. Each NPX tablet contains 500 mg of naproxen, MTH tablet contains 400 mg of methocarbamol, and each OMZ tablet contains 20 mg of omeprazole. Five tablets of each drug were completely pulverized and homogenized, and a suitable weight of the tablet powder was dissolved in 100 ml of distilled water. The ultrasonic waves were used for better dissolution. Then, the samples were filtered through filter paper and the solution was diluted with buffer. The prepared solutions were transferred to electrochemical cells to determine their accurate concentrations using differential pulse voltammetry. The content of naproxen, methocarbamol, and omeprazole in the samples was measured using the standard addition to reduce the matrix effect.

Fig. 1 (**a**) X-ray diffraction spectroscopy pattern of Fe3O4-CuO-ZnO nanoparticles; (**b**) scanning electron microscope image of Fe_3O_4-CuO-ZnO nanoparticles


(a)

(b)

nanocomposites, MWCNT, and MIP, the CPE structure becomes porous and the surface area increases significantly (Figs. 2a and b). The addition of multi-walled carbon nanotubes and magnetic nanoparticles and molecularly imprinted polymer provides a more porous structure for the carbon paste electrode (Noviandri and Rakhmana 2012). This modification results in mesoporous and macroporous structures with large surface areas (Terán-Alcocer et al. 2021). Meanwhile, magnetite nanoparticles have appealed significant interest for the electrodes modification owing to their individual characteristics, such as low toxicity, large surface area, good biocompatibility, robust superparamagnetic properties, and ease of preparation (Akbarzadeh et al. 2012). As mentioned in the literature, nanomagnetite plays an influential role in the electrode processes. For example, it acts as a catalyst to get high peak current densities and

high electro-catalytic activity toward the analytes (Tariq Shah et al. 2018). Substantial decrease in the charge transfer resistance at carbon paste electrodes has also been reported too (Al-Zahrani et al. 2016). Magnetite also causes the stability and selectivity of the electrodes.

Electrochemical behavior of naproxen, methocarbamol, and omeprazole on the surface of modified and unmodified carbon paste electrode

Initially, the electrochemical performance of naproxen, methocarbamol, and omeprazole was investigated by a voltammetric technique using cyclic voltammetry. Figure 3 shows a comparison of cyclic voltammetry in the absence of drugs (a) and the presence of drugs with concentrations of 0.1 mM naproxen, methocarbamol, and omeprazole in

Fig. 2 Images from the scanning electron microscope (SEM): **a** carbon paste electrode. (**b**) Modified carbon paste electrode
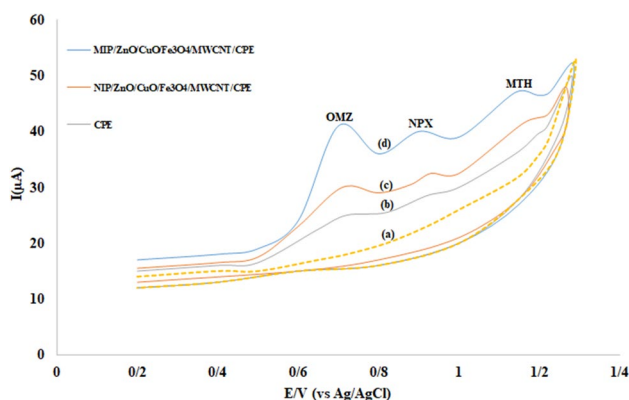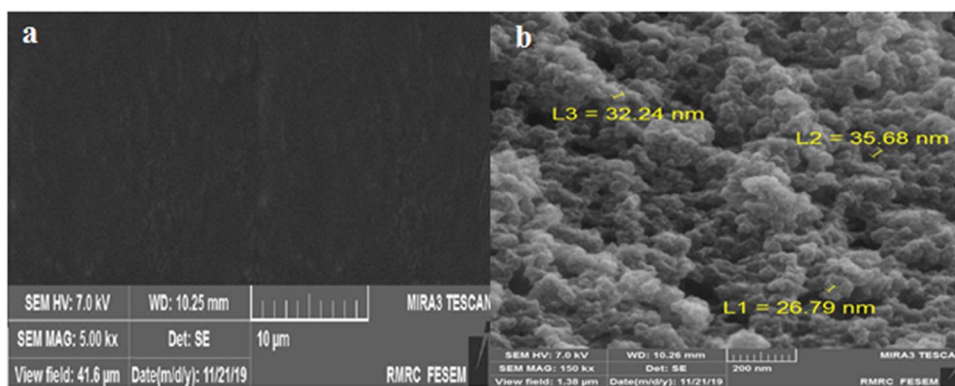
Fig. 3 Cyclic voltammograms (**a**) in the absence of drugs and(**b**) and(**c**) and(**d**) in the surface of carbon paste electrode (CPE) and carbon paste electrode modified with NIP/MWCNTs/Fe₃O₄-CuO-ZnO and modified with MIP/MWCNTs/Fe₃O₄-CuO-ZnO, respectively, in the presence of a 1 mM solution of omeprazole and naproxen and methocarbamol in solution with phosphate M1.0 with pH = 7 and scan speed of 150 mVs

phosphate buffer at pH = 7 with three different electrodes (bare carbon paste (b), modified carbon paste electrode with magnetic nanocomposite/molecularly non-imprinted polymer (NIP) (c), and carbon paste electrode modified with magnetic nanocomposite/molecularly imprinted polymer (d)). The bare carbon paste electrode shows a weak oxidation potential peak at + 0.92 V for naproxen and under the same conditions for methocarbamol and omeprazole at the potential at + 1.16 and + 0.72 V, respectively. These results suggest that the polymer is a molecularly imprinted used in MIP-CPE strongly absorbs drugs from the aqueous solution, while CPE and NIP-CPE electrodes have little or no capability. In fact, in the synthesis step of the molecularly imprinted polymer, the cavities are created in the MIP that are similar in size, shape, and orientation to the functional groups of the drug molecule. The existence of these molecular identification sites has led to a high tendency of analytes to MIP compared to NIP. On the other hand, the functional groups present in the structure of modifier nanocomposites

have led to an increase in the adsorption of drugs on the NIP-CP electrode compared to CPE (Shang et al. 2014). The results also showed that at the surface of the modified carbon paste electrode, the anodic peaks of naproxen, methocarbamol, and omeprazole shifted to potentials of + 0.9, + 1.14 and + 0.69 V, respectively, and the peak current increased. The modified electrode not only increases the effective surface area for oxidation of drug species, but also increases the electron transfer rate between the analyte and the electrode and improves the electrode kinetics.

Electrochemical properties of modified and unmodified electrodes

The effective electrochemical active surface areas of unmodified and modified electrodes were investigated using cyclic voltammetry technique in the presence of $K_4Fe\,(CN)_6$ as the model redox probe. So, the modified electrode was placed in a 6 mM $K_4Fe\,(CN)_6$ solution containing 0.1 mol/L KCl, and the current-voltage curve at different sweep rates were recorded according to the Randles-Swick equation (Eq. 1.) for a The reversible system of the electrode active surface areas was calculated.

$$Ip = (2.69) \times 10^5 n^{3/2} AC\, D^{1/2} v^{1/2} \tag{2}$$

Here, Ip is the anodic peak current, n = 1 is the number of electrons transferred in the process, A is the surface area of the electrode (cm²), D is the molecular diffusion coefficient (cm²s⁻¹), which is equal to 6.5×10^{-6} cm²s⁻¹, C is the concentration of the electroactive species in solution (mol. cm³) and v is the sweep rate (V.s⁻¹). The electroactive levels of carbon paste (CPE), MWCNTs-CPE and Fe₃O₄/ZnO/CuO/MWCNT@MIP-CPE were calculated to be 0.0321 cm², 0.06741, and 0.11556 cm², respectively. The presence of MWCNTs and Fe₃O₄/CuO/ZnO on the electrode surface led into a superior electroactive area (3.6 times higher than CPE) and also presenting a more reversible electrochemical performance comparing to the CPE and MWCNTs/CPE.

Optimization of experimental parameters

Solvent selection in the removal of template molecules

After synthesizing the molecularly imprinted polymer and modifying the carbon paste electrode with it, the template molecules must be removed to create the imprinted cavities. There are several interactions between monomer molecules and template, including hydrogen bonding and electrostatics. There are many methods for removing template molecules in molecularly imprinted polymer, the most important of which is solvent extraction. This is because the solvent can interact strongly with the polymer and dissolve the template. In this study, various solvent systems such as pure water, methanol, acetonitrile–acetic acid mixture (ACN-HOAc, 8:2 v/v), ethanol–acetic acid (ETOH-HOAc, 9:1 v/v), acetonitrile–water mixture (ACN – H_2O, 1:1 v/v), and acetic acid–methanol mixture (HOAc-MeOH, 1:1 v/v) were used. The results showed that the ethanol–acetic acid mixture (9:1 v/v) could completely and rapidly remove the template.

This is because acetic acid has the ability to easily separate target molecules and break weak hydrogen bonds between target molecules and the polymer structure. Also, the presence of ethanol along with acetic acid causes the removal of unreacted functional monomers remaining in the system because all components of polymerization, especially template molecules in ethanol are soluble. Therefore, for the next stages of the study, a solvent containing ethanol–acetic acid (9:1 v/v) was selected. The results are shown in Figure S1.

Optimization and modification of carbon paste electrode composition

The base of carbon paste is usually a mixture of graphite powder and paraffin oil. Carbon paste can be modified by other compounds. In this study, nanocomposite (Fe_3O_4/ZnO/CuO/MWCNT) and synthesized molecularly imprinted polymer (MIP) were used as modifiers to investigate the effect of adding modifiers on electrode performance. Since the type and ratio of compounds are important for electrodes with optimal structure, different amounts of modifier were added to the paste and the electrode was prepared. For accurate comparison, 7 electrodes were prepared. The experiments were repeated three times for each electrode. Table 1 shows the response of different electrodes under similar electrochemical conditions.

To investigate the role of polymer in electrode functionality, the amount of MIP added to the structure of electrodes No.4 to 6 was changed. According to the results, increasing the amount of MIP molecules leads to an increase in the number of sites available for trapping template molecules to a certain degree, and the results are shown in Table 1. By increasing the amount of MIP from 10 to 20%, our findings reflect electrochemical current improvement. However, since the lack of electrical conductivity is a characteristic of MIP molecules, by increasing the amount of molecular imprinted polymers beyond 20%, this effect overcomes the positive effect of active sites, and thereby, current is reduced.

According to the data, both factors, the type of modifier and its amount, played a significant role. The highest current was obtained for the modified carbon paste with both MIP and nanocomposite (Fe_3O_4/ZnO/CuO/MWCNT) modifiers. Therefore, electrode 5 was selected as the optimal electrode.

The application of higher percentages of MIP reduced the electrode response due to the increase in the paste resistance because MIP is a non-conductive polymer. By selecting the optimal amount of polymer, increasing the selectable locations on the electrode surface led to the improved electrode performance.

Accumulation time effect

The accumulation step is a simple and effective step to increase sensitivity. Because the analyte binds to the modified electrode containing MIP, it takes a certain amount of

Table 1 Optimization of carbon paste composition for drug determination

NO	Graphite (%)	NIP (%)	MIP (%)	Paraffin (%)	Zn:Cu:Fe$_3$O$_4$:MWCNTs (%)	OMZ (μA)	NPX (μA)	MTH (μA)
1	75	0	0	25	0	12.35	11.24	13.07
2	70	0	0	25	5	14.12	15.30	14.17
3	50	0	25	25	0	18.8	17.63	
4	60	0	10	25	5	19.37	18.09	17.93
5	50	0	20	25	5	31.54	30.12	29.28
6	45	0	25	25	5	19.12	18.30	21.17
7	50	20	0	25	5	14.12	15.30	14.17

time to obtain the highest enrichment. Therefore, the effect of accumulation time on the Fe$_3$O$_4$/ZnO/CuO/MWCNT@ MIP sensor in the range of 25–200 s in the presence of three drugs was investigated. Figure S2 shows a diagram of the anodic current peak relative to the accumulation time of 25 to 200 s for a 50 μM solution of each drug. After 100 s, the surface of the electrode becomes saturated with drugs and the anodic peak current reaches a constant value. It means that accumulation equilibrium is attained at the electrode–solution interface (Cesarin et al. 2008). Therefore, the time of 100 s was selected as the optimal accumulation time.

Effect of supporting electrolyte and pH on the oxidation peaks of naproxen, methocarbamol, and omeprazole

Due to the importance of the role of support electrolyte in electrochemical reactions, in addition to phosphate buffer, various support electrolytes such as buffer solution including Britton–Robinson and acetate buffer and citrate and phthalate were selected for the study. This study was performed to determine the best support electrolyte to measure the oxidation current of three drugs. The results show that the analytical signal oxidation three drugs were almost identical in acetate buffer and phosphate buffer at the electrode surface, but had better reproducibility in phosphate buffer. Therefore, in subsequent studies, 0.1 M phosphate buffer

(pH = 7) was used to measure the oxidation of naproxen, methocarbamol, and omeprazole at the modified electrode surface (MWCNTs/Fe$_3$O$_4$-CuO-ZnO/CPE/MIP). Also, the effect of phosphate buffer concentration in the two values of 0.1 and 0.05 M was investigated and compared, and sharper peaks were obtained in 0.1 M phosphate buffer (Figure S3).

In this research, a nanocomposite that contains the elements of zinc, copper, iron, and oxygen was used. These elements appeared in their highest oxidation state in the nanocomposite structure, so no oxidation peak related to the modifier was seen in the oxidation range of the three drugs (Fig. 3(a)). The effect of solution pH on the oxidation peak of naproxen, methocarbamol, and omeprazole 0.1 mM in the range of pH = 3–9 was investigated with 0.1 M phosphate buffer at 50 mVs^{-1} scan rate (Fig. 4(A)). According to Fig. 4(B), the oxidation potential of drugs is transferred to negative values with increasing pH. This suggests that protons are involved in oxidation reactions. According to Scheme 2(A), the mechanism of the OMZ oxidation reaction involves the formation of a cationic radical intermediary by the removal of an electron; then, by the loss of a proton, this cationic intermediary reacts with water to produce an irreversible product (Shahrokhian et al. 2015).

According to the structure of naproxen shown in Scheme 2(B), there are two groups of ether and carboxylic acid in the structure of this enzyme inhibitor. As shown in Scheme 2(B), one proton and one electron

Fig. 4 (**A**) DPV voltammogram in the range of pH = 9–3 in 0.1 M phosphate buffer containing 10 μM of OMZ, NPX, and MTH drugs with a scan rate of 150 mVs using a modified carbon paste electrode. MIP/ MWCNTs/Fe$_3$O$_4$-CuO-ZnO (**B**) line graphs related to peak oxidation potential against pH and (**C**) peak oxidation currents of OMZ, NPX, and MTH against different pHs (N = 5)
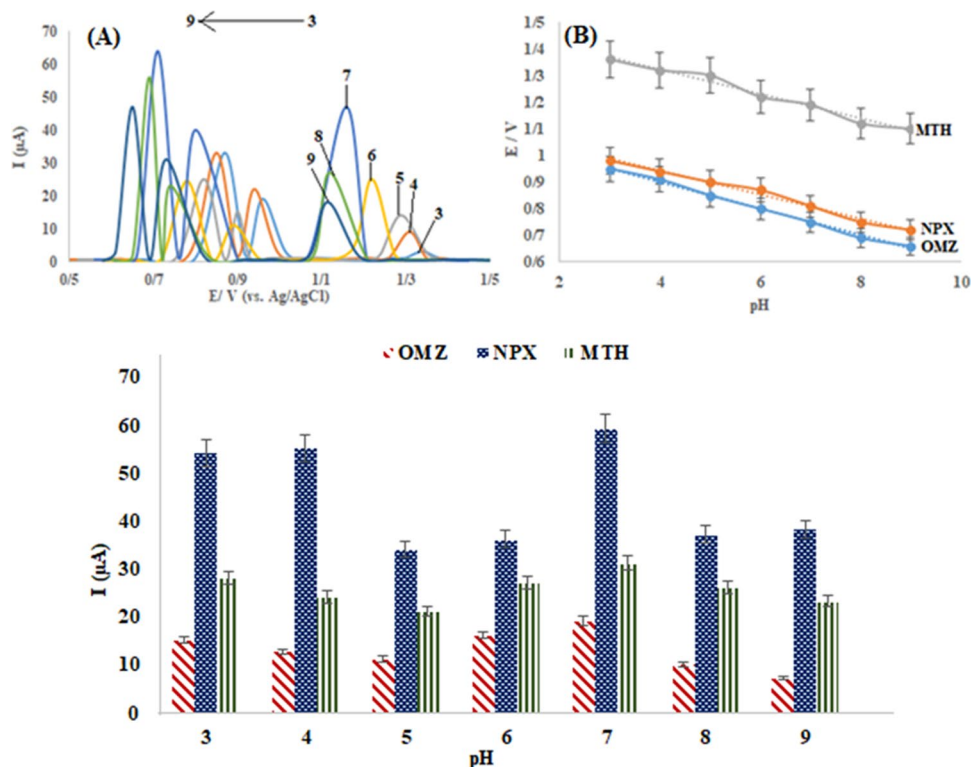
Scheme 2. Proposed oxidation reaction (**A**) omeprazole (OMZ) (**B**) naproxen (NPX) (**C**) methocarbamol (MTH)
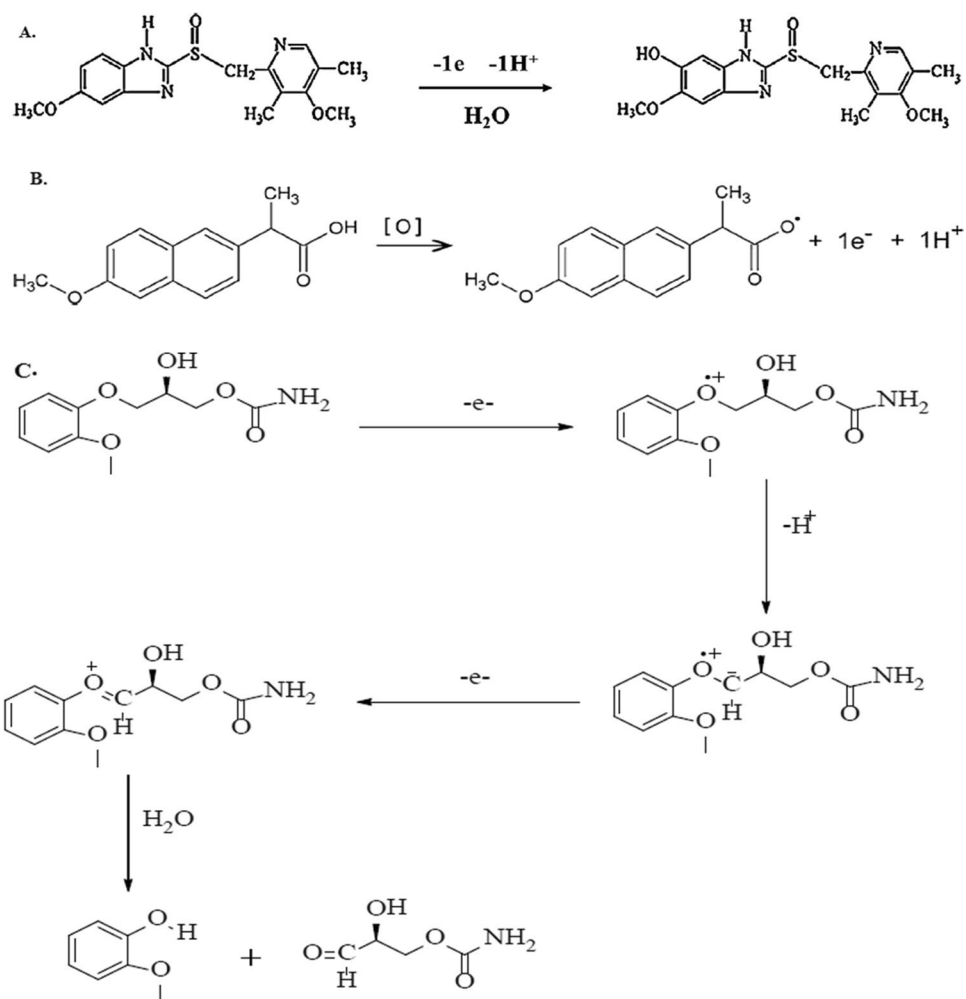
participate in the electrochemical oxidation process of naproxen. This mechanism is also confirmed by the electrochemical methods presented in previous studies (Sarhangzadeh 2015). Methocarbamol has an ether bond in its molecular structure, which is located on the ether oxygen of a non-bonded electron pair that can lose it. Methocarbamol forms a radical cation by losing one electron from this unbonded electron pair then converted to an oxonium ion by losing a proton and an electron. Exonium ions were immediately hydrolyzed to 2-methoxy phenol and 2-hydroxy-3-isopropyl ester. The possible mechanism according to previous studies is shown in Scheme 2(C) (Lamani et al. 2016). Figure 4(C) shows that the peak currents of naproxen and methocarbamol increase to pH = 7, and for naproxen, some increase to pH = 9. But for omeprazole, it changed slightly to pH = 7. Then, with increasing pH, the peak current of the three drugs decreased. At pH < 7, the peaks were small. At pH > 7, drugs disposed to decompose, resulting in a reduced current response. Therefore, pH = 7 was chosen as the best pH (Fig. 4). Oxidation peak potential (Epa)

was linearly related to pH for naproxen, methocarbamol, and omeprazole. According to the Epa versus pH diagram, gradients of -0.0446, -0.0461, and -0.0504 for naproxen, methocarbamol, and omeprazole were obtained based on the following equations:

$$MTH : E_{pa}(V) = -0.0461\,pH + 1.5064; R^2 = 0.9807 \quad (3)$$

$$NPX : E_{pa}(V) = -0.0446\,pH + 1.1207; R^2 = 0.9904 \quad (4)$$

$$OMZ : E_{pa}(V) = -0.0504\,pH + 1.1036; R^2 = 0.996 \quad (5)$$

The slopes of Epa against the pH of the solution are close to the slope of the Nernst equation, which indicates that the number of electrons and protons involved in the oxidation reaction of the drugs are equal. The mechanism of the proposed oxidation reactions of naproxen, methocarbamol, and omeprazole on the modified electrode in 0.1 M phosphate buffer solution (pH = 7) is presented in Scheme 2 (Bojdi et al. 2015; Soltani et al. 2018).

The effect of scan rate on the electrochemical behavior of target drugs using the modified carbon paste electrode

The effect of scan rate on the redox behavior of target analytes was studied. For this purpose, differential pulse voltammograms were drawn at different scan rates in the range of 10 to 300 mV /s and the results are reported in Fig. 5(A). According to Fig. 5(B), there is a linear relationship between the current peak and the square root of the scan rate of all three compounds according to the following equations, which indicate that the oxidation process of the species is under the diffusion process. The linearity is expected for a process that occurs under diffusion control; however, the intercept higher than zero indicates that an additional process other than diffusion occurs during the process. Charge transfer kinetics may also be involved.

$$OMZ : I_p(\mu A) = 3.6498 \, \upsilon^{1/2} \left(V^{1/2}s^{-1/2}\right) - 9.4986; R^2 = 0.9986 \tag{6}$$

$$NPX : I_p(\mu A) = 3.5479 \, \upsilon^{1/2} \left(V^{1/2}s^{-1/2}\right) - 5.8432; R^2 = 0.9989 \tag{7}$$

$$MTH : I_p(\mu A) = 6.2761 \, \upsilon^{1/2} \left(V^{1/2}s^{-1/2}\right) - 11.912; R^2 = 0.9988 \tag{8}$$

In addition, the relationship between $\log i_p$ versus $\log \upsilon$ is as follows:

$$OMZ : \log i_{pa}(\mu A) = 0.8872 \log \upsilon \left(mVs^{-1}\right) - 0.3198 \, (R^2 = 0.999) \tag{9}$$

$$NPX : \log i_{pa}(\mu A) = 0.5563 \log \upsilon \left(mVs^{-1}\right) - 0.6575 \, (R^2 = 0.9989) \tag{10}$$

$$MTH: \log i_{pa}(\mu A) = 0.5611 \log \upsilon \left(mVs^{-1}\right) - 0.4201 \, (R^2 = 0.9963) \tag{11}$$

If the slope of the equations is close to the theoretical value of 0.5, the process is controlled based on the diffusion, and if it is close to one, the electrochemical process is controlled based on the adsorption (Bard and Faulkner

2000). Since the slope of the omeprazole equation is close to 0.8872, the electrode reaction is controlled by adsorption, and if the slope of the NPX and MTH equations is close to 0.5, it can be concluded that the oxidation of the two drugs is mainly controlled by the diffusion process.

Also, the equation of peak current in terms of scan rate for omeprazole is as follows:

$$OMZ:I_p(\mu A) = 3.6616 \, \upsilon \left(Vs^{-1}\right) - 4.7998; R^2 = 0.9838 \tag{12}$$

The above equation confirms that omeprazole is also under the control of adsorption.

Overall, our results show that the oxidation reaction of OMZ on modified CPE is a one-electron and one-proton process and both diffusion and adsorption processes control the electrochemical oxidation pathway of OMZ.

According to the Laviron equation, the irreversible anodic reactions controlled by the diffusion process have a peak potential (E_P) of the following equation (Wu et al. 2004):

$$E_{pa} = E^0 - (RT/(1-\alpha)nF) \ln \left((1-\alpha)nF/RTK_s\right) + (RT/(1-\alpha) nF) \ln \upsilon \tag{13}$$

In this equation, E^0 is the standard formal potential, υ is potential scan rate, α is the electron transfer coefficient, n is the number of exchanged electrons, F is the Faraday constant ($96,493$ C mol^{-1}), R is the gas constant (8.314 J mol^{-1} K^{-1}), T is the temperature (298 K), and K_s is the standard heterogeneous rate constant. Consider that the slope of the E_p curve versus $\log \upsilon$ was 0.0333, 0.045, and 0.053 for OMZ, NPX, and MTH, respectively, and the value of α for irreversible reactions is 0.5. Therefore, the n values for OMZ, NPX, and MTH were 1.184, 1.16, and 0.962, which were approximately equal to one electron for all the target analytes.

Calculation of transfer coefficient (α) and penetration coefficient (D)

The Tafel plot was used to determine the electron transfer coefficient (α). For this purpose, the results related to

Fig. 5 (**A**) DPV voltammogram of a modified carbon paste electrode at different scan rates of 10 to 300 mV / s in a solution of 0.1 M phosphate buffer with pH = 7 containing 1 mM of omeprazole, naproxen, and methocarbamol (**B**) Peak current changes in omeprazole, naproxen, and methocarbamol square root of the scan rate (N = 5)
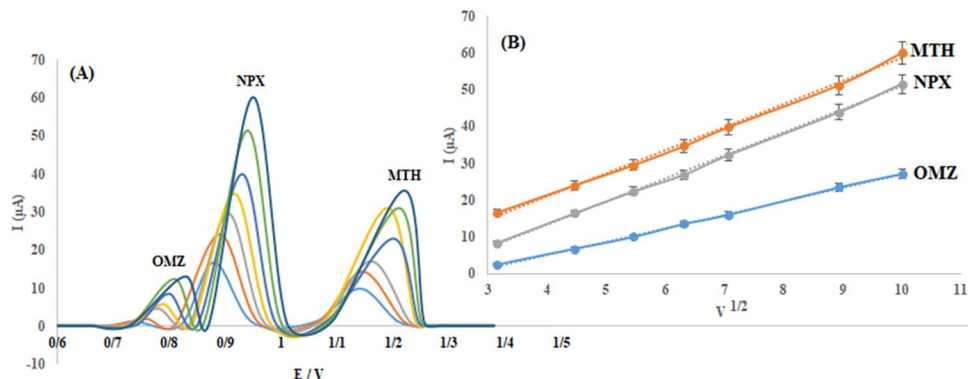
linear scanning voltammograms in which the kinetics control the process (ascending part of the diagram) were used. The slope of the curve log i_p against potential is: n (1-α) F/2.303RT. According to known values for F = 96,493 C mol^{-1}, R = 8.314 J mol^{-1} K^{-1}, and T = 298 K, the value of α is calculated. Figures S4, 5, 6(A) and Figures S4, 5, 6 (B) show the TOEFL diagrams for 50 µM concentrations for OMZ, NPX, and MTH, respectively. The α values for OMZ, NPX, and MTH were 0.76, 0.54, and 0.51, respectively.

To determine the diffusion coefficient of the studied compounds, chronoamperometry method was used. Chronoamperograms are shown in Figures S7(A, B, and C) and S8(A, B, and C), respectively, chronoamperograms Modified electrode With MIP/MWCNTs/Fe$_3$O$_4$-CuO-ZnO in the presence of different concentrations of naproxen and methocarbamol. In order to record chronoamperograms, a potential of 1.1 V was applied. In order to record chronoamperograms of oxidation of naproxen and methocarbamol and to determine the diffusion coefficient, the Cottrell curve of this compound was plotted at different concentrations. As can be seen, the obtained curves are linear according to the Cottrell relation. According to the Cottrell equation:

$$I = nFAD^{1/2}C_b\pi^{-1/2}t^{-1/2} \tag{14}$$

In this relation, n is the exchanged electrons, A is the active surface of the electrode (cm^2), D diffusion coefficient (cm^2.s^{-1}), C is the concentration of the analyzed compound (mmol.L^{-1}), t (s), and F = 96,493 Cmol^{-1}. From its slope, the diffusion coefficient of the electroactive species can be obtained. The slope of the diagram will be equal to nFACD$^{1/2}$ / $\pi^{1/2}$. Figures A-S7 and A-S8 show the naproxen chronoamperogram with concentrations of 0.5, 1, 1.5, and methocarbamol 0.2, 0.7, and 1.4 mM (a-c), respectively.

Current diagrams were plotted against t-1/2 for each of the chronoamperograms, and then, slope plots were plotted I–t$^{-1/2}$ versus concentration for naproxen and methocarbamol. By substituting constant values F, A, π, and n = 1, the diffusion coefficient is equal to 1.085×10^{-5} cm.s^{-1} for methocarbamol and the number of electrons is equal to one electron; 2.42×10^{-6} cm.s^{-1} was obtained for naproxen.

Selectivity of the sensor

In Fig. 6, differential pulse voltammetry response of Fe$_3$O$_4$/ZnO/CuO/MWCNT@MIP and Fe$_3$O$_4$/ZnO/CuO/ MWCNT@NIP sensors for the three drugs in the presence of similar drugs (naproxen like ibuprofen, fenoprofen, gemfibrozil), methocarbamol (methocarbamol like guaifenesin, mephenesin, zonisamide), and (omeprazole like acetaminophen, pantoprazole, phenylalanine) was tested. The results showed that the response of the modified Fe$_3$O$_4$/ZnO/CuO/ MWCNT@MIP CPE for the three drugs naproxen and methocarbamol and omeprazole was higher than similar species. The response of both modified NIP and MIP sensors was almost similar for other species. Therefore, although the structure of these species was similar to drugs, due to the size and functional groups in the cavities, the response of Fe$_3$O$_4$/ZnO/CuO/MWCNT@MIP sensor to drugs was higher than similar species. To evaluate the selectivity of the prepared sensors, the peak current ratio (I_{MIP}/I_{NIP}) was used for the three drugs and other similar species. As the results show, the amount of I_{MIP}/I_{NIP} was higher for the three drugs than for similar species. Also, this ratio is approximately equal to 1 for other species, which indicates the high selectivity of the sensor prepared for the three drugs. The results are depicted in Fig. 6.

Fig. 6 Selectivity differential pulse voltammetry response of sensors prepared with MWCNTs/Fe$_3$O$_4$-CuO-ZnO/NIP and MWCNTs/Fe$_3$O$_4$-CuO-ZnO/ MIP for 20 µM naproxen, methocarbamol, and omeprazole in the presence of other similar species (N = 5)
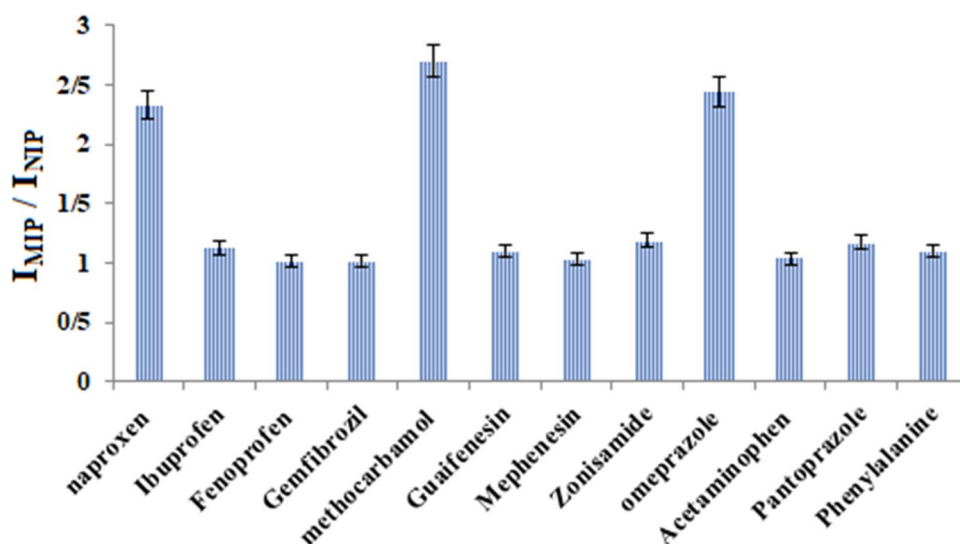
Linear range and detection limit of naproxen, methocarbamol, and omeprazole

The differential pulse voltammetry (DPV) method has a high sensitivity in measurements due to its lower base current and was used to measure analytes under optimal conditions and phosphate support electrolyte (pH = 7). Figure S10(A-i) shows the simultaneous measurement of three compounds in the presence of different concentrations of omeprazole and a constant concentration of 0.4 μM naproxen and 75 μM methocarbamol and the corresponding calibration diagram (Figure S10(A-ii). In this figure, as the concentration of drugs increases, the signal increases, and the peak current versus concentration confirms a suitable linear relationship between peak current and concentration. The line equation is as follows:

$$\text{OMZ: } y = 0.9855x + 0.4243; R^2 = 0.9999 \tag{15}$$

$$\text{NPX: } y = 44.766x + 5.2147; R^2 = 0.9997 \tag{16}$$

$$\text{MTH: } y = 0.1587x + 3.1944; R^2 = 0.9997 \tag{17}$$

And the detection limit of this method (concentration of sample with a signal-to-noise ratio of 3) for omeprazole, naproxen, and methocarbamol was calculated to be 1.8, 1.1, and 0.78 nM, respectively.

Due to the importance of simultaneous measurements of several compounds using modified electrodes, simultaneous measurements of naproxen and methocarbamol and omeprazole were investigated. For this purpose, different concentrations of omeprazole in the presence of constant concentrations of naproxen and methocabamol were investigated by differential pulse voltammetry method in 0.1 M phosphate buffer (pH = 7). Figure S10(A-i) shows the simultaneous measurement of three compounds in the presence of different concentrations of omeprazole and a constant concentration of 0.4 μM naproxen and 75 μM methocarbamol and the corresponding calibration diagram (Figure S10(A-ii)). As can be seen, a continuous change in the concentration of omeprazole without altering the peak current of naproxen and methocarbamol only increases the oxidation current of omeprazole, indicating that simultaneous measurement of this compound is possible without disturbing the other two compounds. Also, simultaneous measurements of three compounds in the presence of different concentrations of naproxen and at constant concentrations of 40 μM omeprazole and 75 μM methocarbamol have been studied. As shown in Figure S10(B-i), a continuous change in naproxen concentration without increasing the peak flow of omeprazole and methocarbamol only increases the oxidation current of

naproxen. The corresponding calibration diagram is plotted (Figure S10(B-ii)). Also, simultaneous measurements of three compounds in the presence of different concentrations of methocarbamol at constant concentrations of 18 μM omeprazole and 0.15 μM naproxen have been studied. As shown in Figure S10(C-i), a continuous change in the concentration of methocarbamol only increases the oxidation current of methocarbamol without altering the peak current of omeprazole and naproxen. The corresponding calibration diagram is drawn (Figure S10(C-ii)).

In the other case, the concentrations of the two species changed and the concentrations of the other drug remained unchanged. In the first case, the concentrations of naproxen and methocarbamol changed and the concentration of omeprazole remained unchanged (Figure S11(c)(b)(a)). In the second case, the concentration of naproxen and omeprazole changed and the concentration of methocarbamol remained unchanged (Figure S11(e)(d)(f)), and in the third case, the concentration of methocarbamol and omeprazole changed and the concentration of naproxen remained unchanged (Figure S11(i)(h)(g)). According to the results of the experiments, a calibration curve was drawn in each case for species whose concentrations changed. The results showed that by changing the concentration of the two drugs, there was no significant change in the peak current and potential peak of other species. Figure 7 shows the differential pulse voltammogram obtained from the modified MWCNTs/Fe$_3$O$_4$-CuO-ZnO/MIP/CPE electrode for the three compounds naproxen, methocarbamol, and omeprazole in conditions where the concentrations of all three species are constantly changing. As can be seen, the separation between the peaks of the three species is such that it is possible to determine each of them separately. Calibration curves are plotted by concentration regression against peak current (Fig. 7(A)).

As shown in Fig. 7-B, the peak oxidation current of omeprazole in the linear range of 5.0 nM to 100 μM and naproxen in the linear range of 5 nM to 100 μM and omeprazole in the linear range of 1.0 nM to 130 μM is proportional to their concentration. The linear regression equations of peak current (i_p) and concentration (M) for the analysis of simultaneous standard solutions of the three drugs are as follows:

$$\text{OMZ: } y = 0.9849x + 1.4753; R^2 = 0.9999 \tag{18}$$

$$\text{NPX: } y = 45.492x + 5.2466; R^2 = 0.9999 \tag{19}$$

$$\text{MTH: } y = 0.1556x + 3.3122; R^2 = 0.9999 \tag{20}$$

Quantitative measurements (LOQ) and detection limit (LOD) were calculated based on the equations
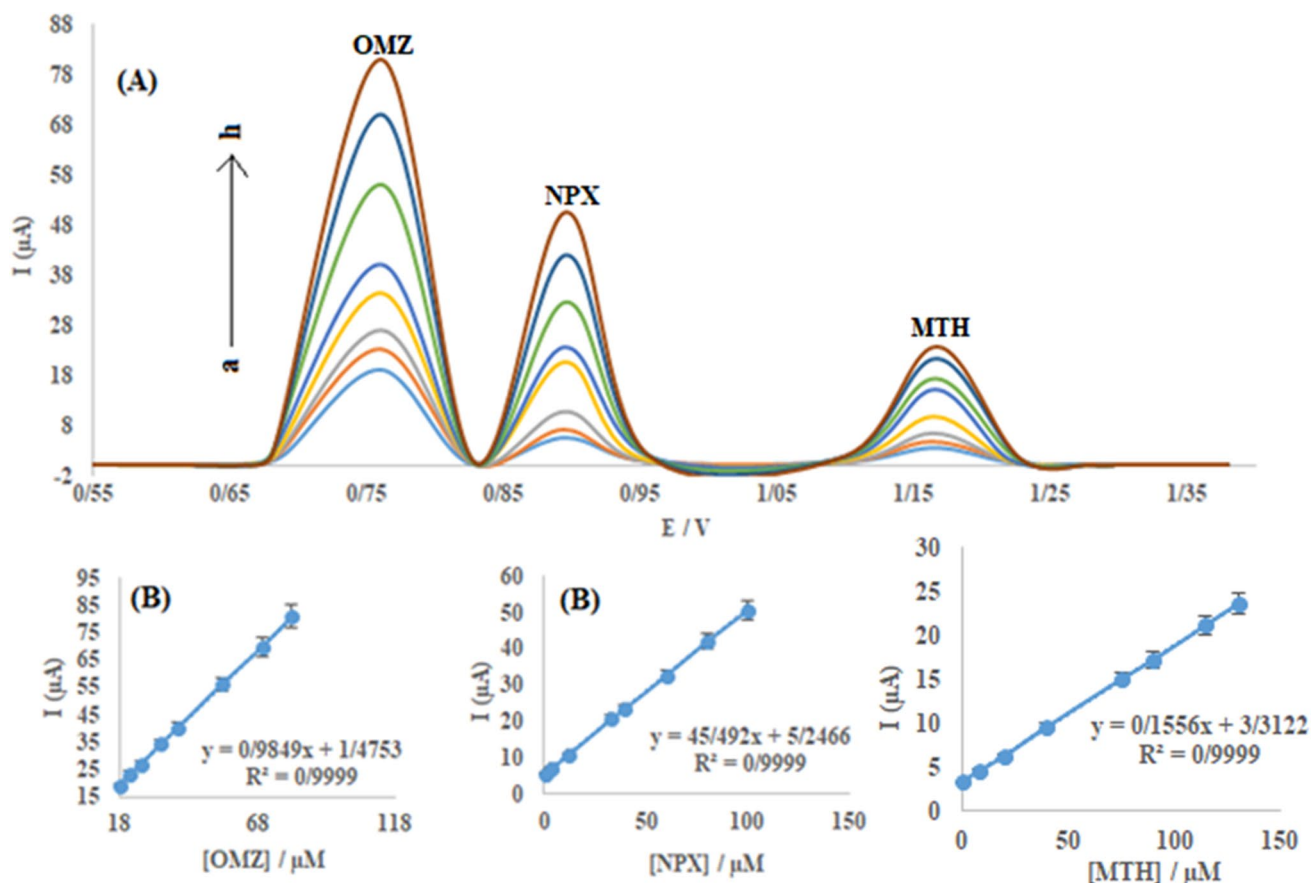
Fig. 7 Differential pulse voltammograms for simultaneous measurement of naproxen (a; 0.005, b; 0.05, c; 10, d; 30, e; 40, f; 60, j; 80, h; 100 μM), methocarbamol (a; 0.001, b; 0.5, c; 20, d; 40, e; 70, f; 90, j; 115, h; 130 μM), and omeprazole (a; 0.005, b; 0.5, c; 10 μM, d; 40, e; 50, f; 60, j; 75, h; 90 μM) species under optimal conditions: 0.1 M phosphate buffer and 50 mVs^{-1} scan rate (N = 5)

LOD = 3 s/m and LOQ = 10 s/m. In these equations, S: standard deviation are different values of peak current for the lowest drug concentrations and m: the slope of the calibration curve. Statistical data from the results of experiments performed for drugs individual and simultaneously with the proposed method are summarized in Table 2. As given in Table 2, there is no significant difference between the LOD and LOQ values of individual and simultaneous measurements of drugs, but the linear range for measurement was only less than three drugs simultaneously. Therefore, the simultaneous measurement of these three drugs has been more efficient with the proposed method.

Table 3 compares the results of this electrode with the other electrodes reported in the scientific literature and shows the performance of the modified carbon paste electrode in the present work for the three drugs naproxen, methocarbamol, and omeprazole. As can be seen, the present electrode shows acceptable and comparable results with other methods performed (Afkhami et al. 2017; Deng et al. 2017; Bojdi et al. 2015; Mutharani et al. 2019; Montes et al. 2014; Santos et al. 2019; Atty et al. 2019).

As given in Table 3, the linear range of the electrode used (Fe$_3$O$_4$/ZnO/CuO/MWCNT@MIP-CPE) is comparable to other sensors and the detection limit of this method is close to the best method mentioned in previous studies. The employed method in this research is proved to be simple, low cost, efficient and does not require advanced technology to fabricate required sensor. It can be used as a suitable alternative to determine naproxen, methocarbamol, and omeprazole in biological samples.

Renewability, reproducibility, stability, and investigation of the interference effects

Renewability for 5 modified electrodes for measuring NPX, MTH, and OMZ with a concentration of 0.01 μM by cyclic voltammetry at a voltage range of 0.2 to 1.3 V and the scan rate of 150 mVs^{-1} in phosphate buffer solution (pH = 7) was investigated. The relative standard deviation (RSD) of five measurements was 1.21% for NPX, 2.23% for MTH,

Table 2 Analytical parameters for electrochemical determination of naproxen, methocarbamol, and omeprazole molecules in 0.1 M phosphate buffer of pH 7.0, and 50 mVs^{-1} scan rate

Serial No	Analyte	LDR/µM	LRE	R^2	LOD/nM	LOQ/nM
(A) Individual determination of OMZ, NPX and MTH:						
1	OMZ	0.018–80	$y = 0.9855x + 0.4243$	0.9999	1.8	5.1
2	NPX	0.005–80	$y = 44.766x + 5.2147$	0.9997	1.1	1.3
3	MTH	0.001–115	$y = 0.1587x + 3.1944$	0.9997	0.78	6.1
(B) Determination of either of the three molecules while keeping concentration of other two constant:						
1	OMZ	0.0180–80	$y = 0.9885x + 0.3325$	0.9999	1.71	5.0
2	NPX	0.005–80	$y = 45.034x + 5.3068$	0.9997	1.0	12.5
3	MTH	0.001–115	$y = 0.1559x + 3.2638$	0.9999	075	5.8
(C) Simultaneous determination of two of the three molecules where the third is kept constant:						
1	NPX	0.004–50	$y = 59.529x + 4.8138$	0.9993	1.0	12.2
	MTH	0.001–115	$y = 18.392x + 5.1021$	0.9996	0.72	6.0
2	OMZ	0.005–100	$y = 59.529x + 4.8138$	0.9993	1.7	5.01
	NPX	0.001–105	$y = 59.529x + 4.8138$	0.9986	1.0	12.1
3	OMZ	0.0035–100	$y = 0.9516x + 7.8727$	0.9993	1.7	5.02
	MTH	0.0015–105	$y = 0.4230x + 2.7066$	0.9986	1.1	5.9
(D) Simultaneous determination of OMZ, NPX and MTH:						
1	OMZ	0.005–100	$y = 0.4230x + 2.7066$	0.9999	1.5	5.3
2	NPX	0.005–100	$y = 0.4230x + 2.7066$	0.9999	1.0	2.8
3	MTH	0.001–130	$y = 0.4230x + 2.7066$	0.9999	0. 7	6.4

Table 3 Comparison of the performance of different modified electrodes for measuring naproxen, methocarbamol, and omeprazole

Electrode	Analyte	LDR/µM	LOD/µM	Method	Ref
Ni$_{0.5}$Zn$_{0.5}$Fe$_2$O$_4$/Gr/GCE[a]	OMZ	0.03–100	0.015	DPV	(Afkhami et al. 2017)
S-MWCNTs–Fe$_3$O$_4$/PDDA[b]/GCE	OMZ	0.05–9	0.015	LSV	(Deng et al. 2017)
Mercapto-NP-F-CPE	OMZ	$2.5 \times 10^{-4} - 25.0$	4.0×10^{-5}	DPV	(Bojdi et al. 2015)
CB-g-PAA/La$_2$O$_3$/GCE [c]	NPX	0.02–888	0.035	DPV	(Mutharani et al. 2019)
MWCNTs/GCE	NPX	1–100	0.6	Amperometry	(Montes et al. 2014)
CD-GrO/CPE[d]	MTH	1.0–50	0.398	SWV	(Santos et al. 2019)
ZY/SDS/MSPE[e]	MTH	0.05–884	0.08	SWV	(Atty et al. 2019)
MIP/MWCNTs/Fe$_3$O$_4$-CuO-ZnO/CPE	OMZ	0.005–100	0.0015	DPV	This work
	NPX	0.005–100	0.001	DPV	
	MTH	0.001–130	0.0007	DPV	

LDR: linear dynamic range; LOD: detection limit

[a] nickel–zinc ferrite (Ni0.5Zn0.5Fe2O4)/graphene (Gr) modified glassy carbon electrode (GCE)

[b] shortened multi-walled carbon nanotubes–Fe$_3$O$_4$ nanoparticles and poly(2,6-pyridinedicarboxylic acid))

[c] carbon black (CB)/poly(acrylic acid/lanthanum oxide nanomaterials/glassy carbon electrode (GCE

[c] carbon black (CB)/poly(acrylic acid/lanthanum oxide nanomaterials/glassy carbon electrode (GCE

[d] graphite oxide (GrO)/β-cyclodextrin (CD)/carbon paste electrode (CPE)

[e] zeolite bulk/sodium dodecyl sulfate/modified screen printed electrochemical sensor

and 2.56% for OMZ. These results showed that the modified electrode has good renewability.

To evaluate the reproducibility of the modified electrode, voltammograms of three drugs with a concentration of 5×10^{-4} M at pH = 7 were performed with the modified electrode for 10 times. Finally, according to the obtained current intensity, the relative standard deviation (RSD %) of the electrode response was calculated. The RSD values of the

electrode response for NPX, MTH, and OMZ were 2.25%, 2.70%, and 1.81%, respectively. The results showed that the reproducibility of the three electrodes was satisfactory.

The stability of the modified electrode during 2.0 months was examined by differential pulse voltammetry at room temperature. The results showed that the response of the modified electrode to the initial response for the compounds decreased by 5% only after 2.0 months, indicating good

stability of the modified electrode. This decrease is probably due to the contamination of the MIP at the electrode surface.

Interferences were measured by comparing current of the certain concentration of the analytes and current of the analytes in the presence of different amounts of the interfering species dissolved in the same analytes solution with a concentration of ten times the analytes.

The modified sensor showed little (< 5% current deviation) or in other words no response to the interfering substances. Results are demonstrated in Fig. 8.

Real sample analysis

To evaluate the performance of the modified electrode in the electrochemical determination of the analytes, human plasma and urine, tap water, and tablets were selected. For this purpose, differential pulse voltammograms were recorded for the real samples before and after spiking. The calibration curve was plotted, and then, the amount and recovery of the analyte in real samples were evaluated. The data are presented in Table 4.

Results shown that the proposed sensor has a high capability to analyze real samples. On the other hand, a comparison of the results obtained from the proposed method with chromatographic methods showed that although sometimes chromatographic methods have a relatively lower detection limit, but it requires a lot of time to prepare samples and devices, also requires expensive reagents and experienced staff. In comparison, our proposed method solves some of these problems. Therefore, this method is suitable for measuring drugs in real samples, especially in drug samples due to the sufficient sensitivity of this alternative method. The detection limits of high-performance liquid chromatography (HPLC) for omeprazole, naproxen, and methocarbamol are

0.19, 0.086, and 1.66 µM, respectively, which is higher than the fabricated sensor LODs proposed in this study (Kamal et al. 2020; Escamilla-Lara et al. 2020; El-Yazbi et al. 2019).

Conclusion

This work describes the construction process of a novel carbon paste electrode that was modified based on Fe_3O_4/ZnO/CuO/MWCNT nanocomposite reinforced triple-template molecularly imprinted polymer-coated layer for determination of omeprazole, naproxen, and methocarbamol. Cyclic voltammetry and differential pulse voltammetry were used for simultaneous measurement of the analytes. To achieve maximum sensitivity, the effect of various chemical and instrumental factors was investigated. Concurrent integration of molecularly imprinted polymer and nanocomposite led to advantages such as increased electron transfer rate, extensive specific surface area, and high specific sites at the electrode surface.

The most important gain of this research over other similar works is the selective measurement of three drugs simultaneously by a nanocomposite reinforced triple-template molecularly imprinted polymer. The modification of the polymer with nanocomposite has made it particularly efficient. It is noteworthy that the rapid response and easy removal of the template are the superior features of the fabricated sensor over the time-consuming and hard washing conditions that usually reported in the literature for the MIPs. The sensor presented a simple and consistent method to detect the analytes with wide potential applications.

Due to these features, simultaneous and selective measurement of analytes was taken in the suitable linear ranges and low detection limits. Therefore, the fabricated carbon

Fig. 8 Evaluation of the effect of interference species with a concentration of ten times the analytes, in the measurement of 0.1 mM omeprazole, naproxen, and methocarbamol by modified carbon paste electrode MIP/MWCNTs/Fe_3O_4-CuO-ZnO
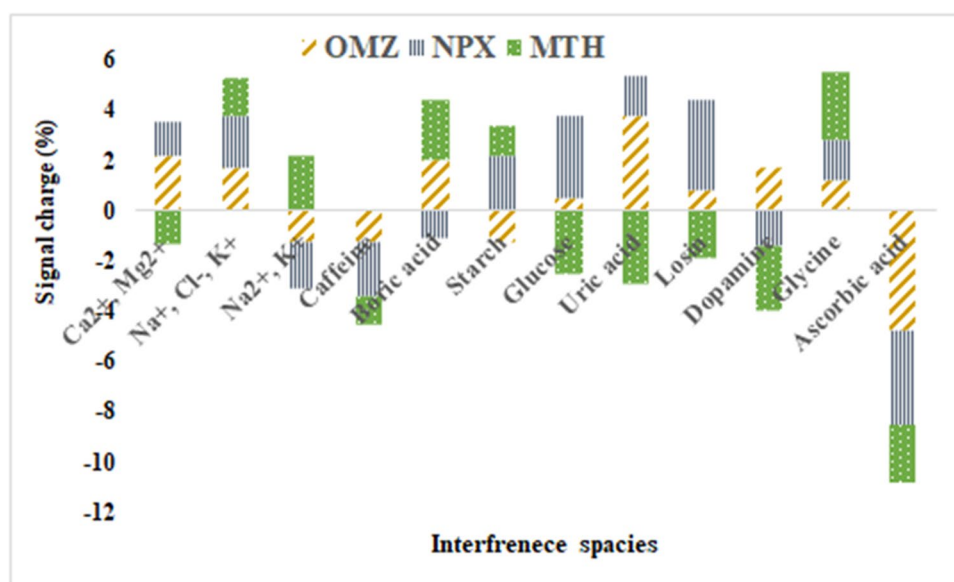
Table 4 Measurement of omeprazole, naproxen and methocarbamol in real samples (n=5)

Sample	Added (μM)			Found (μM)±CL [a]			Recovery (%)			Precision RSD (%)			Accuracy		
	OMZ	NPX	MTH	OMZ	NPX	MTH	OMZ	NPX	MTH	OMZ	NPX	MTH	OMZ	NPX	MTH
Tap water	0.0	0.0	0.0	N.D[b]	N.D	N.D	-	-	-	-	-	-	-	-	-
	10	10	10	9.8±0.01	9.6±0.02	9.92±0.1	98	96	99.2	2.01	3.12	1.29	-2	-4	-0.8
	25	25	25	24.73±0.03	24.8±0.3	24.6±0.02	98.9	99.2	98.4	1.08	1.06	2.42	-1.08	-0.8	-1.6
Plasma	0.0	0.0	0.0	N.D	N.D	N.D	-	-	-	-	-	-	-	-	-
	15	15	15	14.06±0.01	15.03±0.02	14.8±0.01	93.7	100.2	98.6	1.71	3.40	3.01	-6.02	0.2	-1.3
	30	30	30	28.9±0.02	30.5±0.03	29.6±0.02	96.3	101.6	98.6	3.12	2.26	3.59	-3.6	1.6	-1.3
Urine	0.0	0.0	0.0	N.D	N.D	N.D	-	-	-	-	-	-	-	-	-
	20	20	20	19.62±0.03	20.41±0.0	19.8±0.01	98.1	102	96.3	2.13	1.46	3.51	-1.9	2.05	-3.7
	40	40	40	39.62±0.01	39.7±0.01	39.6±0.02	99	99.25	98	3.61	3.11	2.61	-3.6	-0.7	-2
Tablet[c]	0.0	0.0	0.0	5.59±0.03	10.95±0.02	15.95±0.03	96.5	100.9	96.6	2.81	3.51	3.61	-	-	-
	10	10	10	16.08±0.01	20.84±0.02	26.03±0.03	104.9	98.9	100.8	3.58	2.35	2.33	3.14	-0.5	0.3
	20	20	20	24.95±0.04	30.66±0.03	35.69±0.01	96.8	103.3	98.7	3.50	1.53	3.31	-2.5	-0.9	-0.7
like	0.0	0.0	0.0	N.D	N.D	N.D	-	-	-	-	-	-	-	-	-
river	15	15	15	14.88±0.02	15.07±0.01	14.6±0.02	99.2	100.5	97.3	1.68	3.35	3.03	-6.01	0.22	-1.2
water	30	30	30	29.95±0.04	30.56±0.03	29.69±0.01	99.8	101.9	98.9	3.10	2.23	3.51	-3.5	-1.7	-1.3
Pharmaceutical factory effluents	0.0	0.0	0.0	5.69±0.02	10.85±0.03	14.85±0.03	97.5	101	98.3	2.71	3.61	3.31	-	-	-
	10	10	10	16.05±0.02	19.83±0.03	26.13±0.02	107`	98.9	99.15	3.49	2.71	2.23	3.23	-0.6	0.4
	20	20	20	25.15±0.03	31.06±0.02	35.89±0.02	100.6	103.5	102.25	3.53	1.64	3.33	-2.4	-0.8	-0.8

[a]CL: 95% confidence limit, [b]ND: Not detected, [c] Label value (20 mg OMZ and 250 mg NPX and 400 mg MTH)

paste electrode was used as a promising and powerful sensor to effectively oxidize and simultaneously determine omeprazole, naproxen, and methocarbamol in pharmaceutical, biological, and aqueous samples.

Our future fundamental research in the field of electrochemical sensors will focus on use other nanocomposites to modify these electrodes such as graphene and its derivatives and carbon-based quantum dots. It is also accompanied by the development of methods for the synthesis of nanomaterials with ideal properties such as access to more electrically conductivity and more selectivity and specificity for the detection of drugs and environmental contaminants.

Authors Contributions Mohammad Vahidifar carried out investigation and wrote, reviewed, and edited the original draft. **Nader Mansoori Oghaz, Aliakbar Mohammadi,** and **Malihe Samadi Kazemi** were involved in writing, reviewing, and editing. **Zarrin Es'haghi** participated in supervision, writing, reviewing, and editing.

Data Availability All data generated or analyzed during this study are included in this published article.

Declarations

Ethical Approval Not applicable.

Consent to Participate Not applicable.

Consent to Publish Not applicable.

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References

Afkhami A, Gomar F, Madrakian T (2016) nanoparticles modified carbon paste electrode for simultaneous detection of oxycodone and codeine in human plasma and urine. Sens Actuators b: Chem 233:263–271. https://doi.org/10.1016/j.snb.2016.04.067

Afkhami A, Bahiraei A, Madrakian T (2017) Application of nickel zinc ferrite/graphene nanocomposite as a modifier for fabrication of a sensitive electrochemical sensor for determination of omeprazole in real samples. J Colloid Interface Sci 495:1–8. https://doi.org/10.1016/j.jcis.2017.01.116

Akbarzadeh A, Samiei M, Davaran S (2012) Magnetic nanoparticles: preparation, physical properties, and applications in biomedicine. Nanoscale Res Lett 7:144. https://doi.org/10.1186/1556-276X-7-144

Akir S, Barras A, Coffinier Y, Bououdina M, Boukherroub R, Omrani AD (2016) Eco-friendly synthesis of ZnO nanoparticles with different morphologies and their visible light photocatalytic performance for the degradation of Rhodamine B. Ceram Int 42:10259–10265. https://doi.org/10.1016/j.ceramint.2016.03.153

Al-Zahrani E, Soomro MT, Bashami RM, Rehman AU, Danish E, Ismail MI, Aslam M, Hameed A (2016) Fabrication and performance of magnetite (Fe3O4) modified carbon paste electrode for the electrochemical detection of chlorite ions in aqueous medium. J Environ Chem Eng 4:4330–4341. https://doi.org/10.1016/j.jece.2016.09.036

Asadi M, Shabani AMH, Dadfarnia S, Abbasi B (2015) Vortex-assisted surfactant-enhanced emulsification microextraction based on solidification of floating organic drop combined with high performance liquid chromatography for determination of naproxen and nabumetone. J Chromatogr A 1425:17–24. https://doi.org/10.1016/j.chroma.2015.11.005

Atty SA, Ibrahim AH, Hussien EM (2019) Innovative zeolite nanocrystals bulk-modified screen printed electrochemical sensor for simultaneous determination of methocarbamol and paracetamol. Electrochem Soc 166:1483

Bard AJ, Faulkner LR (2000) Electrochemical methods: fundamentals and applications, 2nd edn. John Wiley and Sons, New York

Beitollahi H, Yoonesfar R (2016) Fabrication of a novel electrochemical nanosensor for voltammetric determination of naproxen. Anal Bioanal Chem 8:29–37

Bojdi MK, Behbahani M, Mashhadizadeh MH, Bagheri A, Davarani SSH, Farahani A (2015) Mercapto-ordered carbohydrate-derived porous carbon electrode as a novel electrochemical sensor for simple and sensitive ultra-trace detection of omeprazole in biological samples. Mater Sci Eng C 48:213–219. https://doi.org/10.1016/j.msec.2014.12.006

Carpenter E (1958) Methocarbamol as a muscle relaxant: its clinical evaluation in acute trauma and chronic neurological states. South Med J 51:627–630

Cesarin I, MarinoG MJR, Cavalheiro ETG (2008) Evaluation of a carbon paste electrode modified with organofunctionalised SBA-15 nanostructured silica in the simultaneous determination of divalent lead, copper and mercury ions. Talanta 75:15–21. https://doi.org/10.1016/j.talanta.2007.06.032

Chomisteková Z, Culková E, Bellová R, Melicherˇcíková D, Durdiak J, Timko J, Rievaj M, Tomˇcík P (2017) Oxidation and reduction of omeprazole on boron-doped diamond electrode: mechanistic, kinetic and sensing performance studies. Sens Actuators B 24:1194–1202. https://doi.org/10.1016/j.snb.2016.10.014

Deng K, Liu X, Li C, Hou Z, Huang H (2017) An electrochemical omeprazole sensor based on shortened multi-walled carbon nanotubes- Fe$_3$O$_4$ nanoparticles and poly (2, 6-pyridinedicarboxylic acid). Sens Actuators, B Chem 253:1–9. https://doi.org/10.1016/j.snb.2017.06.117

El-Yazbi FA, Amin OA, El-Kimary EI, Khamis EF, Younis SE (2019) Simultaneous determination of methocarbamol and aspirin in presence of their pharmacopeial-related substances in combined tablets using novel HPLC-DAD method. Drug Dev Ind Pharm 45:265–272. https://doi.org/10.1080/03639045.2018.1535603

Escamilla-Lara KA, Heredia AC, Peña-Alvarez A, Ibarra IS, Barrado E, Rodriguez JA (2020) Magnetic solid-phase extraction based on poly 4-vinyl pyridine for HPLC-FLD analysis of naproxen in urine samples. Molecules 25:2924. https://doi.org/10.3390/molecules25122924

Gholivand MB, Khodadadian M (2011) Rationally designed molecularly imprinted polymers for selective extraction of methocarbamol from human plasma. Talanta 85:1680–1688. https://doi.org/10.1016/j.talanta.2011.06.066

Ghoneim EM, El-Desoky HS (2010) Electrochemical determination of methocarbamol on a montmorillonite-Ca modified carbon paste

electrode in formulation and human blood. Bioelectrochemistry 79:241–247. https://doi.org/10.1016/j.bioelechem.2010.06.005

Gupta VK, Shamsadin-Azad Z, Cheraghi S, Agarwai S, Taher MA, Karimi F (2018) Electrocatalytic determination of L-cysteine in the presence of tryptophan using carbon paste electrode modified with MgO nanoparticles and acetylferrocene. Int J Electrochem Sci 13:4309–4318. https://doi.org/10.20964/2018.05.53

Kamal AH, Marie AA, Hammad SF (2020) Stability indicating RP-HPLC method for simultaneous determination of omeprazole and aspirin in the presence of salicylic acid as degradation product. Microchem J 152:104350. https://doi.org/10.1016/j.microc.2019.104350

Khan NA, Ahmed S, Farooqi IH, Ali I, Vambol V, Changani F, Yousefi M, Vambol S, Khan SU, Khan AH (2020a) Occurrence, sources and conventional treatment techniques for various antibiotics present in hospital wastewaters: a critical review. TrAC, Trends Anal Chem 129:115921. https://doi.org/10.1016/j.trac.2020.115921

Khan AH, Khan NA, Ahmed S, Dhingra A, Singh CP, Khan SU, Mohammadi AA, Changani F, Yousefi M, Alam S (2020b) Application of advanced oxidation processes followed by different treatment technologies for hospital wastewater treatment. J Clean Prod 269:122411. https://doi.org/10.1016/j.jclepro.2020.122411

Khan NA, Khan SU, Ahmed S, Farooqi IH, Yousefi M, Mohammadi AA, Changani F (2020c) Recent trends in disposal and treatment technologies of emerging-pollutants-A critical review. TrAC, Trends Anal Chem 122:115744. https://doi.org/10.1016/j.trac.2019.115744

Kulkarni AS, Balkrishna MV (2012) Method development and validation for the simultaneous determination of omeprazole and domperidone in solid dosage form by RP-HPLC. Int J Pharm Pharm Sci 4:109–114

Kyzas GZ, Nanaki SG, Koltsakidou A, Papageorgiou M, Kechagia M, Bikiaris DN, Lambropoulou DA (2015) Effectively designed molecularly imprinted polymers for selective isolation of the antidiabetic drug metformin and its transformation product guanylurea from aqueous media. Anal Chim Acta 866:27–40. https://doi.org/10.1016/j.aca.2015.01.045

Lamani SD, Teradale AB, Unki SN, Nandibewoor ST (2016) Electrochemical oxidation and determination of methocarbamol at multiwalled carbon nanotubes-modified glassy carbon electrode. Anal Bioanal Electrochem 8:304–317

Li Y, Liu J, Zhang Y, Gu M, Wang D, Dang YY, Li Y (2018) A robust electrochemical sensing platform using carbon paste electrode modified with molecularly imprinted microsphere and its application on methyl parathion detection. Biosens Bioelectron 106:71–77. https://doi.org/10.1016/j.bios.2018.01.057

Lotfy HM, Hegazy MA, Mowaka S, Mohamed EH (2016) Validated spectrophotometric methods for simultaneous determination of Omeprazole, Tinidazole and Doxycycline in their ternary mixture. Spectrochim Acta a: Biomol Spectrosc 153:321–332. https://doi.org/10.1016/j.saa.2015.07.106

Lu CH, Bhattacharjee B, Chen SY (2009) Microwave synthesis of manganese-ion-doped zinc sulfide nano-phosphors using a novel monomer. J Alloys Compd 475:116–121. https://doi.org/10.1016/j.jallcom.2008.08.042

Mageshwari K, Nataraj D, Pal T, Sathyamoorthy R, Park J (2015) Improved photocatalytic activity of ZnO coupled CuO nanocomposites synthesized by reflux condensation method. J Alloy Compd 625:362–370. https://doi.org/10.1016/j.jallcom.2014.11.109

Mbokou SF, Pontié M, Bouchara JP, Tchieno FMM, Njanja E, Mogni A, Pontalier PY, Tonle IK (2016) Electroanalytical performance of a carbon paste electrode modified by coffee husks for the quantification of acetaminophen in quality control of commercialized pharmaceutical tablets. Int J Electrochem 2016:1953278. https://doi.org/10.1155/2016/1953278

Montes RH, Stefano JS, Richter EM, Munoz RAA (2014) Exploring multiwalled carbon nanotubes for naproxen detection. Electroanalysis 26:1449–1453. https://doi.org/10.1002/elan.201400113

Motaharian A, Naseri K, Mehrpour O, Shoeibi S (2020) Electrochemical determination of atypical antipsychotic drug quetiapine using nano-molecularly imprinted polymer modified carbon paste electrode. Anal Chim Acta 1097:214–221. https://doi.org/10.1016/j.aca.2019.11.020

Mutharani B, Ranganathan P, Chen SM, Karuppiah C (2019) Simultaneous voltammetric determination of acetaminophen, naproxen, and theophylline using an in-situ polymerized poly (acrylic acid) nanogel covalently grafted onto a carbon black/La 2 O 3 composite. Microchim Acta 186:1–11. https://doi.org/10.1007/s00604-019-3752-7

Nevado JB, Penalvo GC, Dorado RR (2005) Method development and validation for the separation and determination of omeprazole enantiomers in pharmaceutical preparations by capillary electrophoresis. Anal Chim Acta 533:127–133. https://doi.org/10.1016/j.aca.2004.11.018

Nevado JJB, Penalvo GC, Dorado RMR, Robledo VR (2014) Simultaneous determination of omeprazole and their main metabolites in human urine samples by capillary electrophoresis using electrospray ionization-mass spectrometry detection. J Pharm Biomed Anal 92:211–219. https://doi.org/10.1016/j.jpba.2013.12.020

Noviandri I, Rakhmana R (2012) Carbon Paste Electrode Modified with Carbon Nanotubes and Poly(3-Aminophenol) for Voltammetric Determination of Paracetamol. Int J Electrochem Sci 7:4479–4487

Patil ST, Sundaresan M, Bhoir IC, Bhagwat M (1998) Packed column supercritical fluid chromatographic separation and estimation of acetaminophen, diclofenac sodium and methocarbamol in pharmaceutical dosage forms. Talanta 47:3–10. https://doi.org/10.1016/S0039-9140(98)00045-9

Qu X, Alvarez PJ, Li Q (2013) Applications of nanotechnology in water and wastewater treatment. Water Res 47:3931–3946. https://doi.org/10.1016/j.watres.2012.09.058

Rajabi HR, Zarezadeh A (2016) Development of a new chemically modified carbon paste electrode based on nano-sized molecular imprinted polymer for selective and sensitive determination of naproxen. J Mater Sci Mater Electron 27:10911–10920. https://doi.org/10.1007/s10854-016-5202-1

Sadecka J, Čakrt M, Hercegová A, Polonský J, Skačáni I (2001) Determination of ibuprofen and naproxen in tablets. J Pharm Biomed Anal 25:881–891. https://doi.org/10.1016/S0731-7085(01)00374-0

Sane RT, Samont RS, Nayak VG (1987) Gas chromatographic determination of methocarbamol from pharmaceutical preparations. Indian Drugs 24:196–198

Santos AM, Wong A, Vicentini FC, Fatibello-Filho O (2019) Simultaneous voltammetric sensing of levodopa, piroxicam, ofloxacin and methocarbamol using a carbon paste electrode modified with graphite oxide and β-cyclodextrin. Microchim Acta 186:1–9. https://doi.org/10.1007/s00604-019-3296-x

Sarhangzadeh K (2015) Application of multi wall carbon nanotube–graphene hybrid for voltammetric determination of naproxen. J Iran Chem Soc 12:2133–2140. https://doi.org/10.1007/s13738-015-0690-0

Shah MT, Balouch A, Rajar PPK, Mahar AM, Khan A, Jagirani MS, Khan H (2018) Synthesis of Magnetite Nanoparticles and Its Application As Electrode Material for the Electrochemical Oxidation of Methanol. J Electronic Mater 47. https://doi.org/10.1007/s11664-018-6409-0

Shahrokhian S, Ghalkhani M, Bayat M, Ghorbani-Bidkorbeh F (2015) Voltammetric behavior and determination of trace amounts of omeprazole using an edge-plane pyrolytic graphite electrode. Iran J Pharm Res 14:465–471

Shang L, Zhao F, Zeng B (2014) Sensitive voltammetric determination of vanillin with an AuPd nanoparticles– graphene composite modified electrode. Food Chem 151:53–57. https://doi.org/10.1016/j.foodchem.2013.11.044

Soltani N, Tavakkoli N, Mosavimanesh ZS, Davar F (2018) Electrochemical determination of naproxen in the presence of acetaminophen using a carbon paste electrode modified with activated carbon nanoparticles. CR Chim 21:54–60. https://doi.org/10.1016/j.crci.2017.11.007

Tashkhourian J, Hemmateenejad B, Beigizadeh H, Hosseini-Sarvari M, Razmi Z (2014) ZnO nanoparticles and multiwalled carbon nanotubes modified carbon paste electrode for determination of naproxen using electrochemical techniques. J Electroanal Chem 714:103–108. https://doi.org/10.1016/j.jelechem.2013.12.026

Taufik A, Saleh R (2017) Synthesis of iron (II, III) oxide/zinc oxide/copper (II) oxide (Fe$_3$O$_4$/ZnO/CuO) nanocomposites and their photosonocatalytic property for organic dye removal. J Colloid Interface Sci 491:27–36. https://doi.org/10.1016/j.jcis.2016.12.018

Terán-Alcocer A, Bravo-Plascencia F, Cevallos-Morillo C, Palma-Cando A (2021) Electrochemical Sensors Based on Conducting Polymers for the Aqueous Detection of Biologically Relevant Molecules. Nanomaterials 11:252. https://doi.org/10.3390/nano11010252

Tutunji MF, Qaisi AM, El-Eswed BI, Tutunji LF (2007) Reactions of Sulfenic Acid with 2-Mercaptoethanol: A Mechanism for the Inhibition of Gastric (H+– K+)-Adenosine Triphosphate by Omeprazole. J Pharm Sci 96:196–208. https://doi.org/10.1002/jps.20588

Weng ND, Lee JW, Hulse JD (1994) Development and validation of a high-performance liquid chromatographic method for the determination of methocarbamol in human plasma. J Chromatogr B 654:287–292. https://doi.org/10.1016/0378-4347(94)00010-7

Wu Y, Ji X, Hu S (2004) Studies on electrochemical oxidation of azithromycin and its interaction with bovine serum albumin. Bioelectrochemistry 64:91–94. https://doi.org/10.1016/j.bioelechem.2004.03.005

Xu J, Wang Y, Xian Y, Jin L, Tanaka K (2003) Preparation of multi-wall carbon nanotubes film modified electrode and its application to simultaneous determination of oxidizable amino acids in ion chromatography. Talanta 60:1123–1130. https://doi.org/10.1016/S0039-9140(03)00214-5

Zhu G, Ju H (2004) Determination of naproxen with solid substrate room temperature phosphorimetry based on an orthogonal array design. Anal Chim Acta 506:177–218. https://doi.org/10.1016/j.aca.2003.11.035