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ORIGINAL PAPER

Electrooxidation and determination of some non-steroidal anti-inflammatory drugs on nanoparticles of Ni–curcumin-complex-modified electrode

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Abstract The electrooxidation of several non-steroidal anti-inflammatory drugs (indomethacin, mefenamic acid, and diclofenac) was investigated on nanoparticles of Ni–curcumin-complex-modified glassy carbon (n-GC) electrode in alkaline solution. Surfaces studies were performed by scanning electron micrographs and atomic force microscopy. The oxidation process and its kinetics were studied using cyclic voltammetry and chronoamperometry techniques and also pseudo-steady-state polarization measurements. Voltammetric studies indicated that, in the presence of drugs, the anodic peak current of low-valence nickel species increases, followed by a decrease in the corresponding cathodic current. This pattern indicates that drugs were oxidized on the redox mediator immobilized on the electrode surface via an electrocatalytic mechanism. A mechanism based on the electrochemical generation of Ni (III)-active sites and their subsequent consumption by drugs was proposed. The rate constants of the catalytic oxidation of drugs and the electron-transfer coefficient are reported. A sensitive, simple, and time-saving amperometric procedure was developed for the analysis of these drugs in bulk form and for the direct assay of tablets, using the n-GC electrode.

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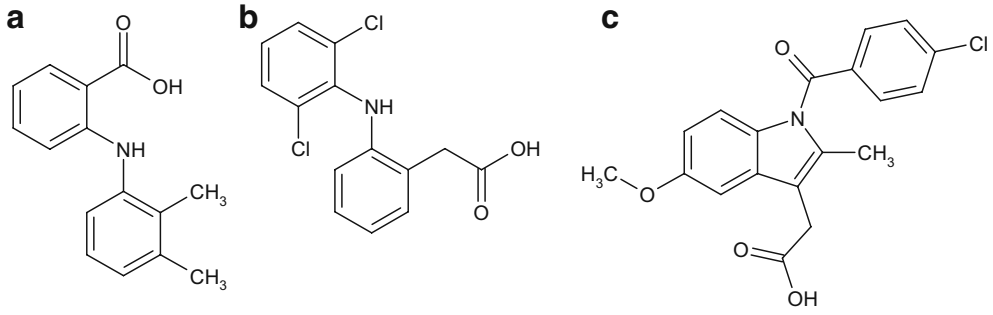
Keywords Anti-inflammatory drug · Electrocatalysis · Nanoparticle · Curcumin · Modified electrode

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) alleviate pain by counteracting the cyclooxygenase (COX) enzyme. On its own, COX enzyme synthesizes prostaglandins, creating inflammation. In whole, the NSAIDs prevent the prostaglandins from ever being synthesized, reducing or eliminating the pain [1]. These drugs have shown anti-inflammatory, analgesic, and antipyretic activities and are usually used in the treatment of inflammatory and degenerative diseases of the articulations [2].

Mefenamic acid (2-[(2,3-dimethylphenyl) amino] benzoic acid, Scheme 1a), diclofenac ([2-[(2,6-dichlorophenyl) amino]phenyl]acetic acid, Scheme 1b), and indomethacin (1-(*p*-chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetic acid, Scheme 1c) are important non-steroidal anti-inflammatory drugs used to treat several pathologies [1]. Mefenamic acid blocks certain substances in the body that are linked to inflammation. It is used in cases of mild to moderate pain, including headache, dental pain, post-operative and post-partum pain, and in musculoskeletal and joint disorders such as osteoarthritis [3]. Diclofenac works by reducing chemicals in the body that cause pain and inflammation. It is used as an adjuvant in the treatment of chronic diseases such as arthritis and glaucoma and is also used to treat osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. Indomethacin is a more powerful drug and is extensively used because of its excellent pharmaceutical properties to relieve the symptoms of ankylosing spondylosis, osteoarthritis, rheumatoid arthritis, and gout.



Scheme 1 **a** Chemical structure of mefenamic acid. **b** Chemical structure of diclofenac. **c** Chemical structure of indomethacin

Owing to the importance of anti-inflammatory drugs in pharmaceuticals and their widespread use, efforts have been made towards the development of simple and reliable analytical methods. Several methods have been reported in the literature to determine anti-inflammatory drugs and their behavior in pharmaceutical preparations and biological samples, including UV spectrophotometry [4], liquid chromatography [5–7], fluorescence spectrometry [8], and gas chromatography–mass spectrometry [9]. However, these techniques are time-consuming or require expensive and sophisticated instruments. Some electrochemical techniques have also been studied [10–14].

Electrochemical techniques have been shown to be excellent procedures for the sensitive determination of organic molecules, including drugs and related molecules in pharmaceutical dosage forms and biological fluids [10–20]. As a rule, many active compounds in dosage forms, in contrast to excipients, can be readily oxidized or reduced. The advance in experimental electrochemical techniques in the field of analysis of drugs is due to their simplicity, low cost, and relatively short analysis time compared with the other techniques. Hence, sample preparation usually consists in dissolving the active compound from the pharmaceutical dosage forms in a suitable solvent and performing a direct analysis on an aliquot of this solution. The specificity and selectivity of the voltammetric techniques are usually excellent because the analyte can be readily identified by its voltammetric peak potential.

Chemically modified electrodes have attracted much interest in the study of the electrocatalytic reaction of many important compounds. Modified electrodes can be prepared by deposition of various compounds such as organic compounds, conducting polymers, metal oxides, etc. on the various electrode surfaces. In the recent years, electrodes coated with metallated electroreactive polymers have received increased attention [21–23]. Indeed, recent researches in developing new electrode materials seem to be directed towards the use of macrocyclic complexes in the form of immobilized complexes that behave as fast-electron-transfer mediators for solution species. Although electrochemistry and electrocatalytic properties of macrocyclic complexes of some transition metals have been well studied [21–24], few data about their behavior as electropolymerized films in aqueous alkaline solution exist. Recently, it has been shown that nickel macrocyclic complexes can be easily electropolymerized onto an electrode surface to form modified electrodes that catalyzed oxidation of several substrates [21–23]. Chemically modified electrodes with nickel compounds were also developed by deposition of nickel metal, nickel oxide, or nickel complexes on a traditional electrode surface via chemical, electrochemical, or physical routes [14, 16, 20, 22–24].

Continuing our recent studies on the design of some modified electrodes aiming at inspection of the electrocatalytic reactions of some biologically important compounds and drugs [14–20, 23], in the present paper, we investigated the electrocatalytic oxidation and also determination of three anti-inflammatory drugs on a glassy carbon (GC) electrode modified with nanoparticles of Ni–curcumin, which to the best of our knowledge, have never been successfully conducted.

Experimental section

Chemicals

All chemicals used in this work were purchased from Merck as analytical-reagent-grade chemicals. The drugs involved were obtained as a gift from the Center of Quality Control of Drug, Tehran, Iran. All solutions were prepared by doubly distilled water.

Instruments

Electrochemical measurements were carried out in a conventional three-electrode cell powered by an electrochemical system comprising an AUTOLAB system with PGSTAT 30 (Eco Chemie, Utrecht, The Netherlands). The system was run on a PC using GPES 4.9 software. A saturated Ag/AgCl and a platinum disk (both from Azar Electrode Co., Iran) were used as reference and counter electrodes, respectively.

Surface morphological studies were carried out using scanning electron microscopy (SEM), using a Philips instrument, Model X-30. Atomic force microscopy (AFM) was performed in ambient conditions using Veeco instrument, Model CP-research operating in contact mode.

Procedures

The standard solutions of authentic drugs were prepared by dissolving an accurate mass of the bulk drugs in an appropriate volume of 100-mM NaOH solution (which was also used as supporting electrolyte) and then stored in the dark at 4 °C. Additional dilute solutions were prepared daily by accurate dilution just before use. The drug solutions were stable and their concentrations did not change with time.

The GC electrode was further polished on a polishing textile pad with a 0.05-μm α-alumina slurry, washed with distilled water, immersed in HNO_3 1:1, and then sonicated in water/acetone mixture for 5 min before modification. Nanoparticles of Ni(II)–curcumin complex were formed on the GC surface by the methods previously reported [21, 23]. Briefly, the GC electrode was placed in 100-mM NaOH solution containing 10 mM curcumin and 4 mM Ni(II)–ammonia complex and applying the potential between 200 and 650 mV with a potential sweep rate of 100 mV s^{-1} in a cyclic voltammetry regime. One hundred potential cycles were applied for the modification of electrode surface. The modified electrode has been denoted as n-GC throughout the text.

The calibration curves for the drugs in 100-mM NaOH solution were measured with an amperometric technique. Working potential of 580 mV was used in amperometric measurements, in which the transient currents were allowed to decay to steady-state values. All studies were carried out at room temperature.

For analysis of tablets, the average mass of ten tablets was determined. The tablets were finely powdered and homogenized in a mortar. An appropriate accurately weighed amount of the homogenized powder was transferred into a 100-mL calibrated flask containing 50 mL of 100-mM NaOH solution. The contents of the flask were sonicated for 10 min; the undissolved excipients were removed by filtration and then diluted to volume with the same supporting electrolyte. Appropriate solutions were prepared by taking suitable aliquots of the clear filtrate and diluting them with 100-mM NaOH solution.

Results and discussion

The progress of the electrodeposition of Ni(II)–curcumin nanoparticles from synthesis solution was monitored as consecutive cyclic voltammograms and shown in Fig. 1. In the preliminary stages of potential cycling (Fig. 1, inset A), an irreversible peak appears that is due to curcumin oxidation. After around 15 potential cycling, a pair of peaks appears which indicates formation of an electroreactive film formed on the surface and the corresponding currents rise during further cycling. After 100 potential cycles, the voltammogram represented in Fig. 1, inset B, is attained. The voltammogram shown is similar to those previously reported [21, 23], and the redox transition involved is attributed to the presence of Ni(II)/Ni(III) species immobilized on the surface. Figure 2 shows the SEM of n-GC electrode surface with different magnifications. Ni–curcumin complex as nanoparticles with an average diameter of 150 nm was immobilized on the electrode surface.

In order to obtain further details of the surface structure, such as thickness and roughness, AFM was used. Figure 3 shows an AFM topology of the surface of n-GC electrode corresponding to 2D (Fig. 3a) and 3D (Fig. 3b) images recorded over an area of 3×3 μm. The 2D image of n-GC electrode surface consists of continuous small clusters smoothly grown on the entire surface containing spherical granules. The existence of <150-nm-size particles at n-GC surface is clearly reflected in 3D AFM image which is characterized by nearly knoll-type projection in the *z*-direction. Furthermore, the thickness of Ni–curcumin film attached to the GC surface is >100 nm. In addition, a

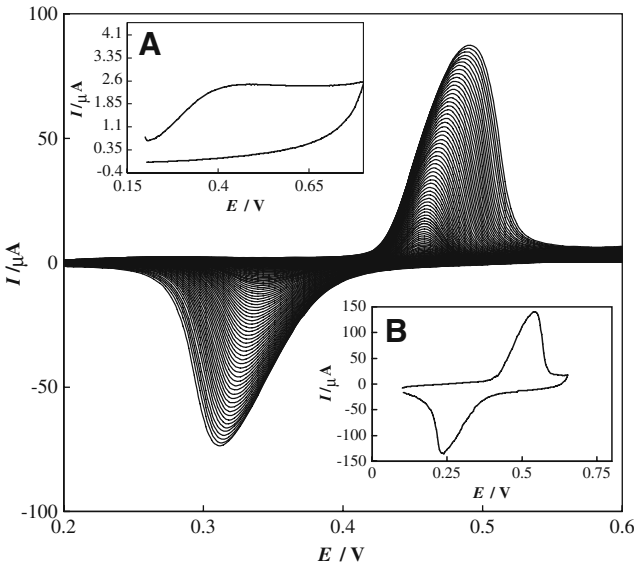


Fig. 1 *Main panel*: Consecutive cyclic voltammograms of 100-mM NaOH solution containing 10 mM curcumin and 4 mM Ni(II)–ammonia complex using a GC electrode. Potential sweep rate was 100 mV s^{-1}. The cycle number increases from inner to outer. *Inset A*: The first cycle in the main panel. *Inset B*: Typical cyclic voltammogram of n-GC obtained after 100 potential cycles in 100-mM NaOH solution. Potential sweep rate was 50 mV s^{-1}

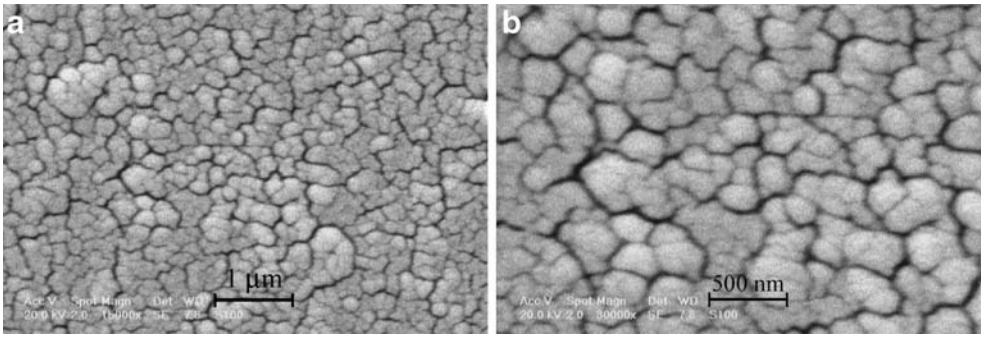


Fig. 2 Scanning electron micrographs of the surface of n-GC with *lower* (**a**) and *higher* (**b**) magnifications

parameter commonly used to quantitatively characterize the surface films is the surface roughness which can be represented by the root-mean-square roughness (standard deviation of the surface height within the given area). This parameter can be determined from AFM images. In the current research, the obtained root-mean-square roughness for the cobalt oxide film is 10.5 nm.

The charge-transfer processes at the n-GC electrode/solution interface and its kinetic (which ion penetration across the film/solution interface is also involved) was previously investigated [23] based on the Laviron's equation [25] and Tafel analysis [26]. We obtained that, in the regime of cyclic voltammetry, n-GC electrode represents a charge-transfer-controlled process at low potential sweep rates in the bulk of film comprising the Ni(II)–curcumin nanoparticles. At high potential sweep rates, however, a charge-transport-controlled process in the bulk of solution is dominated [23].

The effect of pH on the electrochemical behavior of n-GC electrode was investigated. Figure 4a represents cyclic voltammograms of n-GC electrode in the potential range of active nickel moiety recorded at different pH of the solution. As pH decreases, the peak potential related to Ni(II)/Ni(III) transition shifts positively, and the corresponding peak currents decrease. This indicates that proton is involved in the immobilized redox species and also that the nanoparticles are stable only in highly alkaline solutions and, at lower pH, it deactivated or dissolved into the solution. The dependencies of peak potentials and peak currents on pH of the solution are represented in Figure 4b, c, respectively. The slopes of peak potentials on pH of the solution are near the Nernstian value and it witnesses the participation of one proton in the redox transition of Ni(II)/Ni(III).

Figure 5a shows cyclic voltammograms of n-GC electrode obtained in the absence (a) and presence of 0.5 mM mefenamic acid (b), diclofenac (c), and indomethacin (d) using a potential sweep rate of 50 mV s^{-1}. Similar cyclic voltammograms recorded using GC are also shown in Fig. 5b–d. At GC electrode, the drugs are electroreactive and represent an anodic peak. At n-GC electrode, however, oxidation of drugs resulted in a typical electrocatalytic response: the anodic charge increased with respect to that observed for the modified surface in the absence of drugs and it was followed by decreasing the cathodic current upon increasing the concentration of drugs in solution. In addition, the anodic currents at n-GC electrode are very larger than those obtained at GC electrode and the peak potentials in the case of mefenamic acid and diclofenac are shifted to the lower values. The cathodic current that ensued from the oxidation processes in the reverse cycle

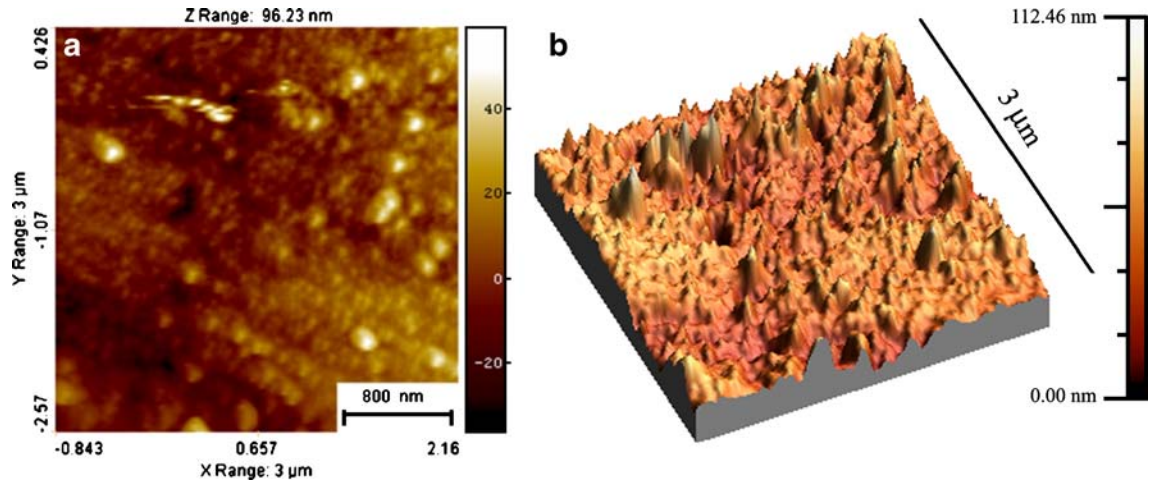


Fig. 3 2D (**a**) and 3D (**b**) AFM topology of the surface of n-GC electrode

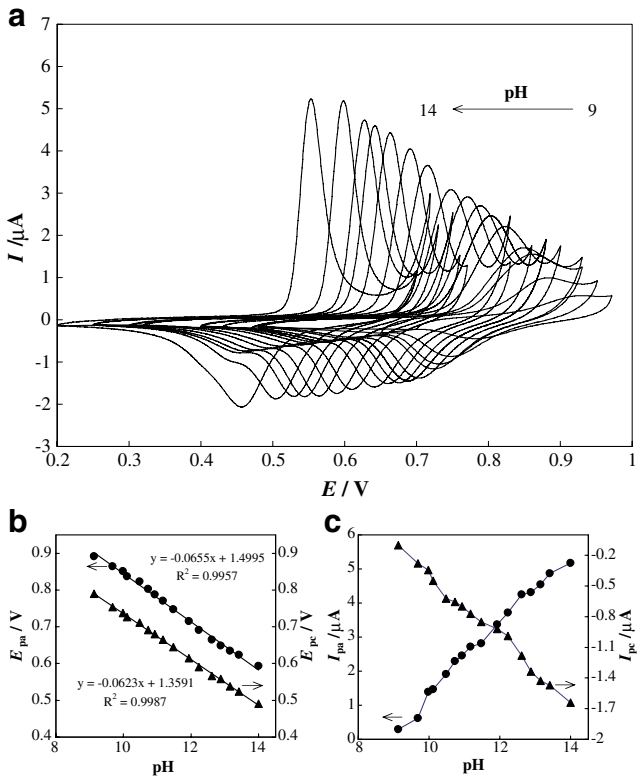


Fig. 4 **a** Cyclic voltammograms of n-GC electrode recorded at different pH of 9–14. **b** Dependency of peak potentials on pH. **c** Dependency of peak currents on pH

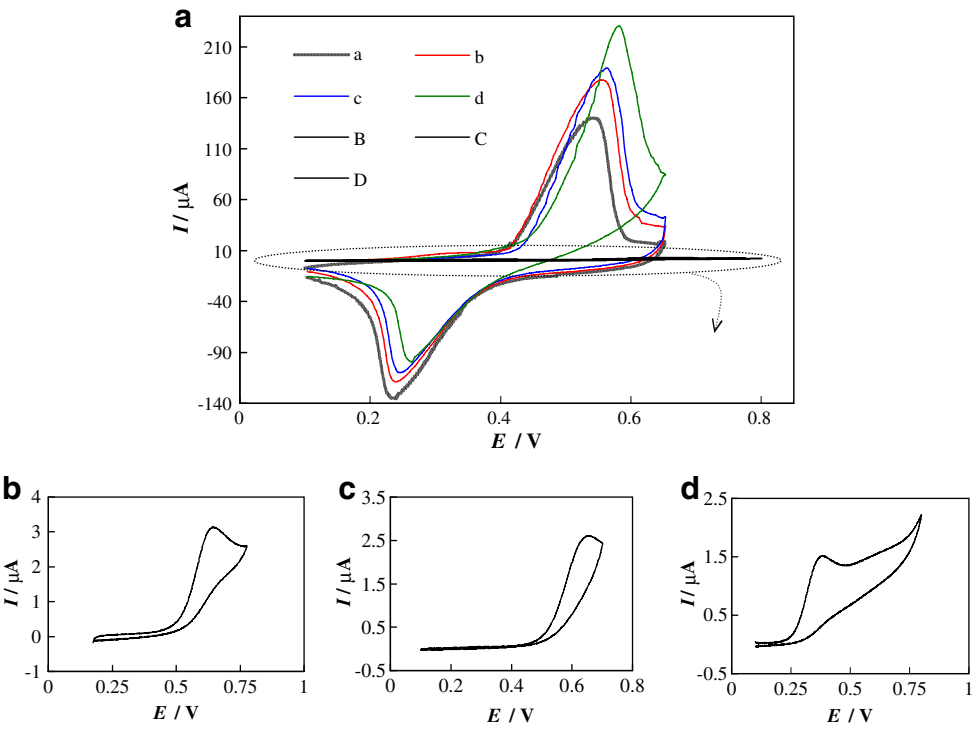
indicates that the rate-determining step certainly involves the drugs and was incapable of reducing the entire high-valence nickel spices formed in the oxidation cycle. Also, plotting the current function (peak current divided by the square root of the potential sweep rate) against the square root of the potential sweep rate (derived from cyclic voltammograms recorded at different potential sweep rate in the presence of drugs) revealed negative slope confirming the electrocatalytic nature of the process (data not shown). Another point in Fig. 5a is that no anodic peak appeared in the reverse (negative) sweep which may be seen in the course of the anodic oxidation of some organics on modified electrode surface [14, 23]. This indicates that no fouling effect occurred during electrooxidation of the drugs. These result indicated that the drugs are oxidized by the active nickel moiety via a cyclic mediation redox process and the following mechanism can be proposed:

$$\mathrm{Ni(II)} \rightleftarrows \mathrm{Ni(III)} + \mathrm{e} \quad (1)$$

$$\mathrm{Ni(III)} - \mathrm{curcumin} + \mathrm{Drug} \xrightarrow{k_{\mathrm{cat}}} \mathrm{products(s)} + \mathrm{Ni(II)} - \mathrm{curcumin} \quad (2)$$

This mechanism based on electrochemical production of Ni(III)-active sites on the electrode surfaces. Accordingly, drugs are oxidized via an EC' mechanism.

Fig. 5 **a** Cyclic voltammograms of n-GC electrode recorded in the absence (*a*) and presence of 0.5 mM mefenamic acid (*b*), 0.5 mM diclofenac (*c*), and 0.5 mM indomethacin (*d*). Potential sweep rate was 50 mV s^{-1}. Curves *B*–*D* are cyclic voltammograms of GC electrode recorded in the presence of 0.5 mM mefenamic acid, 0.5 mM diclofenac, and 0.5 mM indomethacin, respectively. **b** Cyclic voltammograms of GC electrode recorded in the presence of 0.5 mM mefenamic acid. Potential sweep rate was 50 mV s^{-1}. **c** Cyclic voltammograms of GC electrode recorded in the presence of 0.5 mM diclofenac. Potential sweep rate was 50 mV s^{-1}. **d** Cyclic voltammograms of GC electrode recorded in the presence of 0.5 mM indomethacin. Potential sweep rate was 50 mV s^{-1}



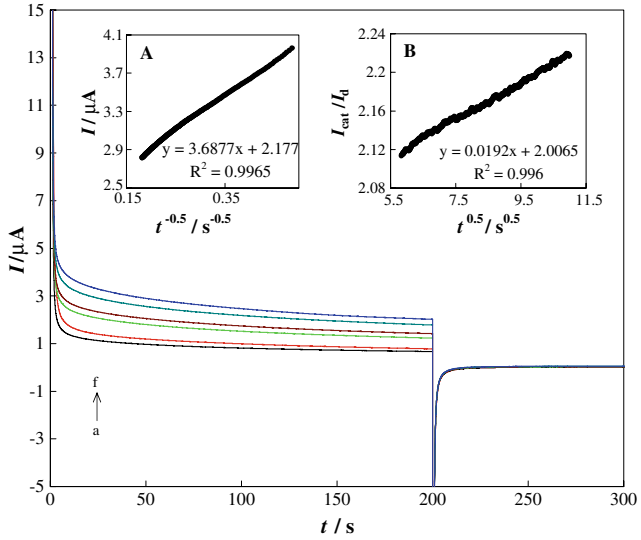


Fig. 6 *Main panel*: Double-step chronoamperograms of n-GC electrode in 100-mM NaOH solution with different concentrations of indomethacin of: *a* 0, *b* 0.04, *c* 0.10, *d* 0.45, *e* 1.0, and *f* 3.93 mM. Potential steps were 600 and 125 mV, respectively. *Inset A*: Dependency of transient current on $t^{-0.5}$. *Inset B*: Dependence of I_{cat}/I_d on $t^{0.5}$

The major pathway for the anodic oxidation of mefenamic acid and diclofenac which have diphenylamine structures can be the formation of the corresponding diphenylamine radicals followed by coupling the radicals [27]. Indomethacin and also diclofenac as substituted carboxylic acids can be oxidized via cleavage of carbon–carbon bond of C–COO and formation of the substituted benzoic acids [28].

Figure 6 shows double-step chronoamperograms of n-GC electrode in the absence (a) and presence (b–f) of indomethacin. The applied potential steps were 600 and 125 mV, respectively. Plotting the net current with respect to the minus square roots of time, presented a linear dependency (Fig. 6, inset A). By using the slope of this line, the diffusion coefficient of drug can be obtained according to Cottrell's equation [29]:

$$I = nFAD^{1/2}C\pi^{-1/2}t^{-1/2} \tag{3}$$

Similar chronoamperograms were recorded for mefenamic acid and diclofenac and the diffusion coefficients of drugs were found and reported in Table 1. The values of diffusion coefficients are in agreement with those reported previously [14]. Chronoamperometry was also used for the evaluation of the catalytic rate constant according to [29]:

$$I_{cat}/I_d = \gamma^{1/2}\left[\pi^{1/2}\mathrm{erf}\left(\gamma^{1/2}\right) + \exp\left(-\gamma/\gamma^{1/2}\right)\right] \tag{4}$$

where I_{cat} and I_d are the current in presence and absence of drug; $\gamma = k_{cat}Ct$ is the argument of the error function; k_{cat} is the catalytic rate constant and t is the elapsed time. In the case where $\gamma > 1.5$ and $\mathrm{erf}(\gamma^{1/2})$ is almost equal to unity, the above equation can be reduced to:

$$I_{cat}/I_d = \gamma^{1/2}\pi^{1/2} = (k_{cat}Ct)^{1/2}\pi^{1/2} \tag{5}$$

From the slope of the I_{cat}/I_d versus $t^{1/2}$ plot (Fig. 6, inset B), the mean values of k_{cat} for indomethacin was found and reported in Table 1. Similar chronoamperograms were recorded for mefenamic acid and diclofenac and the corresponding values of k_{cat} were reported in Table 1.

Electrocatalytic reactions can take place via an electrochemical reaction involving immobilized redox species on the electrode surface followed by a chemical reaction between the substrate in the solution and the active moiety of the redox species [14–16, 19, 20, 23]. This is the EC' mechanism or the mechanism of cyclic mediation electron-transfer process. We have recently developed a kinetic model based on this mechanism for the electrocatalytic oxidation of some biologically active compounds on some modified electrode surface and the faradaic current was calculated [14, 20]. According to that model, the electrode surface is covered only by the redox species. These species can in principle flip-flop between various valence states under the effect of external electric fields and the chemical reaction occurred at the surface of the modified electrodes/

Table 1 The electrocatalytic reaction rate constants (k_{cat}) and the diffusion coefficient (D) obtained from chronoamperometry and the electron-transfer coefficient (α) obtained from Tafel plots for electrocatalytic oxidation of drugs on n-GC electrode

Drug	k_{cat} ($\times 10^{-5}$)/cm^3 mol^{-1} s^{-1}	D ($\times 10^{6}$)/cm^2 s^{-1}	α
Indomethacin	1.19	3.53	0.33
Mefenamic acid	0.24	6.51	0.46
Diclofenac	1.88	1.33	0.59

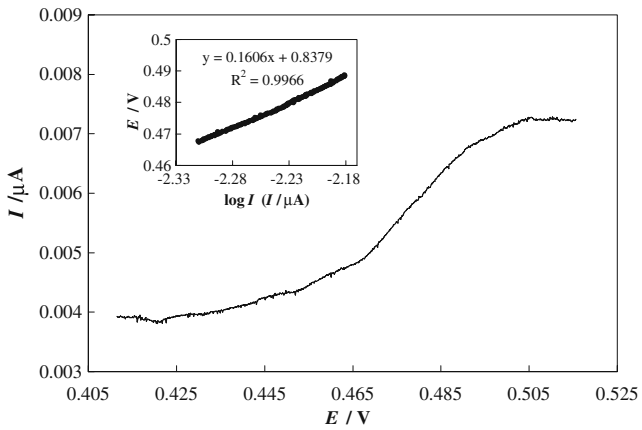


Fig. 7 Pseudo-steady-state polarization curves for n-GC in 100-mM NaOH solution in the presence of 0.5 mM indomethacin. *Inset*: the corresponding Tafel plot

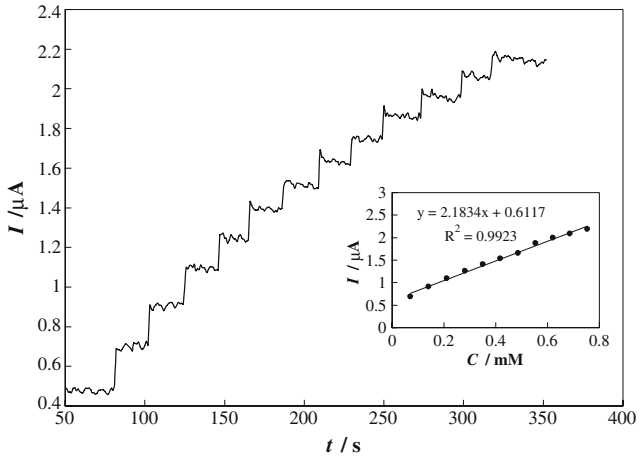


Fig. 8 Current signal as a function of time in 100-mM NaOH solution during repetitive injections of indomethacin using n-GC. Applied potential was 580 mV. *Inset*: Dependency of the transient current on indomethacin concentration

solution interface. Usually, the steady-state approximation for the reaction intermediates is dominated and the reaction is under the control of charge transfer. Also, at high overpotentials, the diffusion of the substrate in the solution can be dominated [14, 20]. Based on that model, there is not a direct relationship between the catalytic current and the catalytic rate constant and both forward and backward rate constants of the redox transitions of the mediator are involved in the current [14, 20]. The conditions described for this model is also dominated for this study. Along this line, the value of catalytic rate constant for diclofenac is higher than that of indomethacin, while catalytic current of oxidation generated for the same concentration for the former drug is lower than the latter drug (see Table 1 and Fig. 5). Based on the model, the values of the catalytic rate constant and forward and backward rate constants for the redox transitions of the mediator can change in a manner that they generate a higher catalytic current for a reaction with the lower catalytic rate constant and vice versa.

Figure 7 shows typical pseudo-steady-state current–potential curve recorded for the electrocatalytic oxidation of indomethacin. A typical S-shaped plot has been obtained

Table 3 Determination of indomethacin, diclofenac, and mefenamic acid in commercial tablets (n=5)

Drug	Amount labeled (mg)	Amount found (mg)	RSD (%)	Bias (%)
Indomethacin	75	71.3	3.8	−4.9
Mefenamic acid	250	240	2.6	−4.0
Diclofenac	100	105	3.4	5

These contain many or all of the following substances/materials: microcrystalline cellulose, magnesium stearate, talc, colloidal silicon dioxide, cellulose, titanium dioxide, hydroxypropylmethylcellulose, and polyethylene glycol

and the electron-transfer coefficient (α) can be found by plotting E vs. log I. Similar current–potential curves were recorded for mefenamic acid and diclofenac and the corresponding values of α for the drugs were summarized in Table 1.

Figure 8 represents typical amperogram obtained for n-GC electrode during the successive addition of indomethacin into 100-mM NaOH solution at an applied potential of 580 mV. The inset of this figure shows the calibration curve obtained, in which a good linear dependency is observed. Similar amperograms were recorded for mefenamic acid and diclofenac. The limits of detection (LOD) and quantitation (LOQ) were calculated according to the $3\times SD/m$ and $10\times SD/m$ criterions for LOD and LOQ, respectively, where SD is the standard deviation of the intercept, and m is the slope of the calibration curves [30]. The values of the analytical parameters obtained for these drugs according to this method were reported in Table 2. It should be noted that the relative standard deviation (RSD) values reported in this table are with the same electrode. No serious fouling effect (related to the adsorption of reaction intermediates/products at the electrode surface) was observed in the course of analysis of the drugs (see also Fig. 5a)

The applicability of the proposed amperometric method to the sample dosage form was examined by analyzing the tablets. It was found that the drug concentrations determined using this method are in good agreement with the

Table 2 The determined parameters for calibration curves of drugs and accuracy and precision (n=3) for electrocatalytic oxidation of drugs on n-GC electrode

	Indomethacin	Mefenamic acid	Diclofenac
Linear range (μM)	384–1,380	384–1,525	196–1,525
Slope (μA mM^{-1})	2.18±0.38	1.99±0.26	2.46±0.23
Intercept	0.50±0.19	0.65±0.15	0.61±0.25
LOD (μM)	74.9 (13.6 [19], 1.41 [14])	95.9 (3.42 [19], 4.96 [14])	27.9 (31.7 [14], 23.0 [31], 99.0 [32])
LOQ (μM)	249.7	319.7	93.0
RSD (%)	3.25	4.63	1.92

The values reported in parentheses are those reported in the literature and the corresponding references appeared in brackets

reported values. The values of the experimentally determined drugs and the declared values of the drugs in tablet form were listed in Table 3.

Selectivity of the amperometric procedure for the analysis of the drugs was examined in the presence of some common excipients in the same ratios usually used in pharmaceutical preparations (e. g., microcrystalline cellulose, magnesium stearate, talc, colloidal silicon dioxide, cellulose, titanium dioxide, hydroxypropylmethylcellulose). The results showed no significant interference from excipients; thus, the procedure was able to assay the drugs in the presence of excipients. Therefore, the method can be considered selective.

To verify the durability and long-term stability of n-GC electrode, 100 consecutive cyclic voltammograms using this electrode were recorded in 100-mM NaOH solution (data not shown). It was found that the peak currents changed slightly (<4%). In addition, the electrode was stored in 100-mM NaOH solution when not in use and retained its electroreactivity for 3 weeks.

Conclusion

A glassy carbon electrode modified with nanoparticles of Ni–curcumin complex was checked for electrooxidation of mefenamic acid, indomethacin, and diclofenac in alkaline medium. The electrode electrocatalytically oxidized these drugs. Chronoamperometric studies demonstrated an anodic current at the oxidation potential of low-valence nickel species, in further support of the mediated electrooxidation. Using steady-state polarization measurements and chronoamperometry technique, we determined the kinetic parameters of these drugs, such as charge-transfer coefficient, catalytic reaction rate constant, and diffusion coefficient dominated in the course of electrooxidation reaction. An amperometric procedure was successfully applied to the quantification of these drugs in bulk and commercial tablets forms.

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