Kinetic Study of the Electrooxidation of Mefenamic Acid and Indomethacin Catalysed on Cobalt Hydroxide Modified Glassy Carbon Electrode

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Electrocatalytic oxidation of two anti-inflammatory drugs (Mefenamic acid and Indomethacin) was investigated on a cobalt hydroxide modified glassy carbon (CHM-GC) electrode in alkaline solution. The process of oxidation and its kinetics were established by using cyclic voltammetry and chronoamperometry techniques as well as steady state polarization measurements. Voltammetric studies indicated that in the presence of under study drugs, the anodic peak current of low-valence cobalt species increased, followed by a decrease in the corresponding cathodic current. This result indicates that the drugs were oxidized *via* cobalt hydroxide species immobilized on the electrode surface *via* an EC mechanism. A mechanism based on the electrochemical generation of Co (IV) active sites and their subsequent consumption by the drugs in question was also investigated. The constants rate of the catalytic oxidation of the drugs and the electron-transfer coefficients reported.

Key Words: Mefenamic acid, Indomethacin, Electrocatalysis, Modified electrode, Alkaline media

Introduction

Modified electrodes have recently received a great deal of interest, largely because they have a wide range of potential applications in electrochemical technology, energy conversion, and particularly, chemical analysis, as well as possible applications in information storage, electrochromism devices, and displayers.[1-3] Of particular interest in this regard is the immobilization of surface-active materials that can, in principle, alternate between various valence states under the effect of external electric fields, and that are capable of mediating fast electron transfer between a substrate in the bulk of the solution and the electrode surface.

Immobilized cobalt ions based materials, which can, in principle, flip-flop between various valence states under the effect of external electric field on the one hand and the potential reducing agent on the other, are of particular interest. The preparation, characterization, and electrochemistry of cobalt hydroxide (oxide) containing films have been extensively studied in alkaline medium.[4,5] Various methods of preparation, ranging from spray pyrolysis,[6] sonication,[7] and sputtering[8] to electrodeposition from aqueous solutions containing complexing agents with various pH values; have been considered.[9-11] Meanwhile, little attention has been paid to the electrocatalytic activities of cobalt hydroxide (oxide) modified electrodes in the electrooxidation of drugs.

Drug analysis has an extensive impact on public health. Electrochemical techniques have been used for the determination of a wide range of drug compounds. They have the advantage of not requiring, in most instances, derivatization, and they are less sensitive to matrix effects than other analytical techniques. Electrochemical techniques also include determination of the drug's electrode mechanism. Redox properties of drugs can provide insight into their metabolic fate, their in vivo redox processes, and their pharmacological activity.[12-15]

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed agents worldwide to treat a variety of pain-related conditions, including arthritis and other rheumatic diseases. In addition, epidemiological studies have shown that long-term use of NSAIDs reduces the risk of developing Alzheimer disease and delays its onset.[16-18] Acetylsalicylic acid (ASA) has anticoagulant properties and prevents strokes and heart attacks (reduction of cardiovascular risks).[19,20] ASA is frequently used for the treatment of fever, minor pain, and it is widely used over the counter (OTC) drug. NSAIDs are included in many cold and allergy preparations. Piroxicam and mefenamic acid are used mainly to treat rheumatoid arthritis and osteoarthritis.[21,22] Mefenamic acid has also been found to produce closure of patient ductus arteriosus in premature neonates.[23] The combination of aspirin-mefenamic acid as an analgesic is more effective than both drugs alone.[24]

Indomethacin is metabolized *in vivo*. It is a powerful drug and is extensively used because of its excellent pharmaceutical properties. It is used to relieve the symptoms of ankylosing spondylitis, osteoarthritis, rheumatoid arthritis, and gout. In addition to its analgesic activity, indomethacin promotes the constriction of patent ductus arteriosus in newborns (a blood vessel called the ductus arteriosus fails to close normally in an infant soon after birth and the blood bypass the lungs).[25]

Dosing is dependent on the postnatal age (PNA) of the infant at the time of therapy initiation because indomethacin clearance is directly proportional to PNA.[26] Shaffer *et al.*[27] have reported that the use of pharmacokinetic/pharmacodynamics to individualize indomethacin dosing allows clinically

diagnosed (patent ducts arteriosus) PDA to be permanently closed in 91% of patients treated; this is higher than the current dosing standards that have a 60-70% of closure rate. Because of the characteristic inter-individual variability of indomethacin pharmacokinetics, it would be desirable to adjust individual indomethacin dosages according to the plasma indomethacin concentration after the first dose. IND is efficiently absorbed following oral administration, with plasma concentration peaking after 1-4 h; it is extensively bound to plasma proteins (90%) and has wide intersubject variability in its elimination half-life.[28-30] However, it has undesirable side effects, such as gastroinstem testinal, bleeding and exacerbation of renal inadequacy.[31] Therapeutic indomethacin level is 3 mg/mL.[32]

Mefenamic acid is used to relieve the symptoms of many diseases such as rheumatoid arthritis, non-articular rheumatism, and sport injuries.[33] It is used to treat mild to moderate pain, including headache, dental pain, post-operative and post-partum pain, dysmenorrhoea, as well as musculoskeletal disorders and joint disorders such as osteoarthritis.[34]

Overdoses of MFA produce toxic metabolite accumulation that causes acute hepatic necrosis, inducing morbidity and mortality in humans. Due to the vital importance of the assay of MFA for pharmaceutical formulations and biological fluids, several analytical methods have been developed for the quantitative determination of this drug in both pharmaceutical and biological samples. Therapeutic mefenamic acid level is 10 μg/mL.[32]

The purpose of the present work is the detailed investigation of Mefenamic acid and Indomethacin oxidation on cobalt hydroxide modified glassy carbon electrode (CHM-GC) in alkaline solution aiming at the elucidation of the kinetics and the derivation of the rate constants.

Experimental

Sodium hydroxide used in these work was of analytical grade from Merck, and was used without further purification. All solutions were prepared by doubly distilled water. The standard solutions of authentic drugs were prepared by dissolving an accurate mass of the bulk drugs in an appropriate volume of 100 mM sodium hydroxide 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 the passing time.

Electrochemical measurements were carried out in a conventional three-electrode cell (from Goldis Co., Iran) powered by an electrochemical system comprising of an AUTOLAB system with PGSTAT30 board (Eco Chemie, Utrecht, The Netherlands). The system was run on a PC using GPES 4.9 software. A saturated calomel electrode (SCE) and a platinum wire (from Azar Electrode Co., Iran) were used as reference and counter electrodes, respectively. The working electrode is glassy carbon with surface area 0.125 cm^2. Modification of the working electrode was carried out by cycling the potential of the electrode in the range of −250 to 750 mV *vs.* SCE electrode. Steady state data were collected after polarization time of 3 min.

Results and Discussion

Cyclic voltammetry. Figure 1A presents 75 consecutive cyclic voltammograms (CV) of a GC electrode in the presence of 100 mM Na_2CO_3, 40 mM NaK tartrate, 4 mM $CoCl_2$ at pH = 11.6 recorded at a potential sweep rate of 100 mV s^{-1}. The voltammograms are similar to those reported in literature.[10,11] Figure 1B shows a cyclic voltammogram of CHM-GC electrode in 100 mM NaOH solution in the range of −200 to 690 mV recorded at a potential sweep rate of 100 mV s^{-1}. It consists of anodic peak located at 225 and 550 mV/SCE which are attributed to Co (II)/ Co (III) and Co (III)/ Co (IV) redox transition associated with different cobalt oxide species on the electrode surface. The cathodic peaks at 186 and 522 correspond to the reduction of various cobalt oxide species formed during the positive sweep.[35,36]

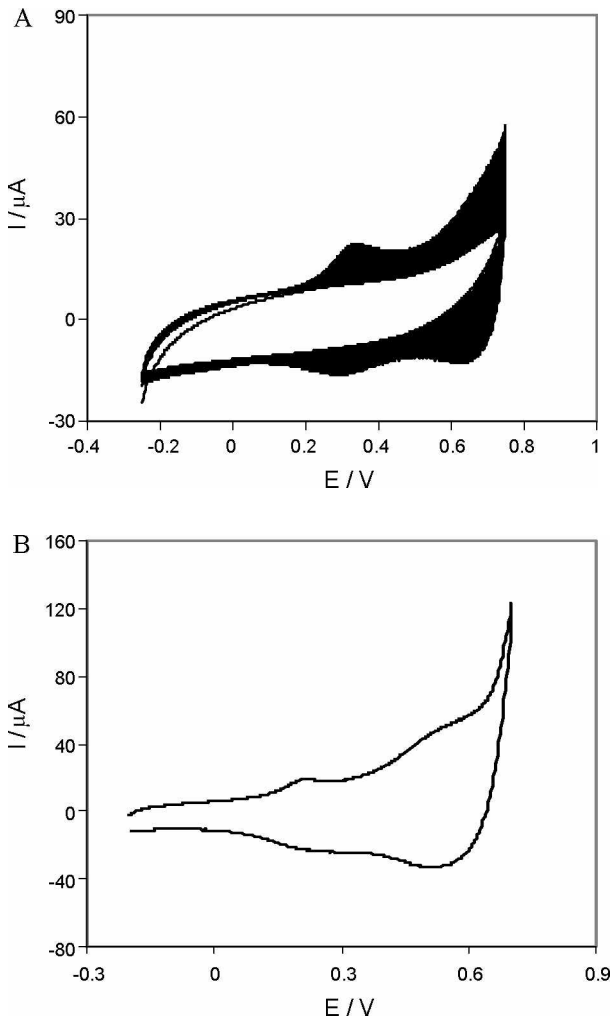


Figure 1. A: cyclic voltammograms for 4 mM $CoCl_2$ + 40 mM Na-K tartrat + 100 mM Na_2CO_3 using a GC electrode, the potential was scanned continuously at 100 mVs^{-1} between −250 and 750 mV. **B**: cyclic voltamograme of CHM-GC in 100 mM NaOH solution in the range of −200 to 690 mV/SCE with a sweep rate 100 mVs^{-1}.

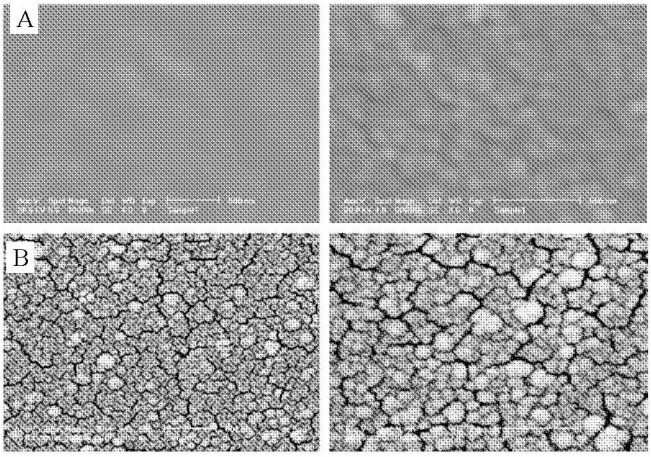


Figure 2. scanning electron micrographs of the surface of bare GC electrode (a) and the surface of CHNM-GC electrode (b).

To investigate the surface morphology of the cobalt hydroxide film formed on the GC surface, it was examined by scanning electron microscopy. The results show that considerable amounts of cobalt hydroxide nanoparticles with an average size of 100 nm were formed on the surface of GC electrode.

Figure 3A presents typical CVs of a CHM-GC electrode in 100 mM NaOH solution at various potential sweep rates of 2-150 mV s^{-1}.

The peak's currents in the range of 2-75 mV s^{-1} are proportional to sweep rates. Figure 3(b) and (c). pointing to the electrochemical activity of the surface redox couple. From the slope of this line and using:

$$I_p = \left(\frac{n^2F^2}{4RT}\right)\nu A\Gamma^* \qquad (1)$$

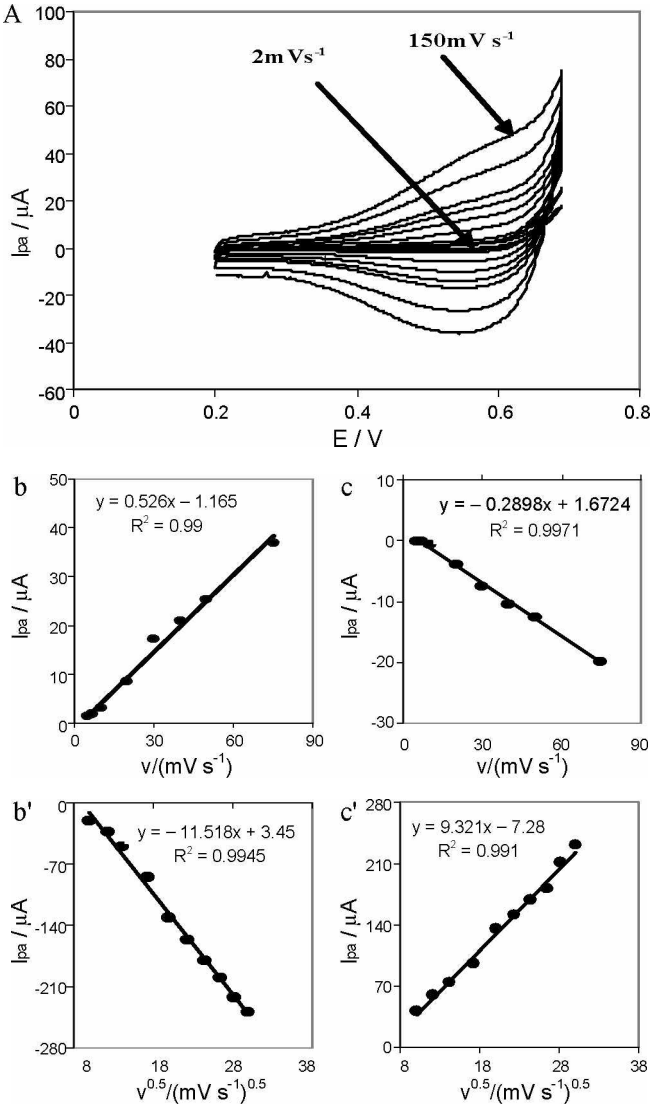


Figure 3. A: Typical cyclic voltammograms of a CHM-GC electrode in 100 mM NaOH in the potential sweep rates of 2, 5, 7, 10, 20, 30, 40, 50, 75, 100, 150 mV s^{-1} (a), the dependency of anodic (**b**) and cathodic (**c**) peak currents to the sweep rate at lower values (2-75 mV s^{-1}) and the proportionality of anodic (**b'**) and cathodic (**c'**) peak currents to the square roots of sweep rate at higher values (100-900 mV s^{-1}).

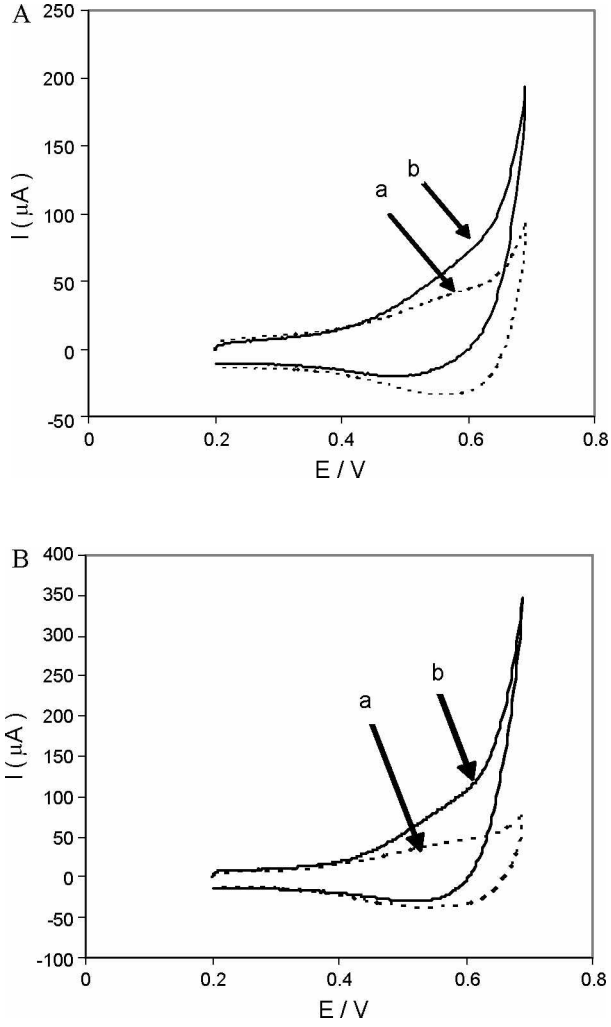


Figure 4. A: Cyclic voltammograms of the bare GC electrode in 100 (mM) NaOH solution in the the presence of 0.1 (mM) of mefenamic acid (a). Cyclic voltammograms of the CHM-GC electrode in 100 (mM) NaOH solution in the the presence of 0.1 (mM) of mefenamic acid (b). **B**: Cyclic voltammograms of the bare GC electrode in 100 (mM) NaOH solution in the the presence of 0.1 (mM) of indomethacin (a). Cyclic voltammograms of the CHM-GC electrode in 100 (mM) NaOH solution in the the presence of 0.1 (mM) of indomethacin (b).

where Γ^* is the surface coverage of the redox species and v being the potential sweep rate[37] and taking average of both cathodic and anodic results. Γ^* values of around $(1.98 \pm 0.02) \times 10^{-9}$ mol cm^{-2} have been derived. In the high range of sweep rates this dependency is of square root form, shown in figures 3b' and 3c', signifying the dominance of the diffusion controlled processes.

Figure 4A, B presents the CVs of GC (a) and CHM-GC (b) in the presence of 0.3 (mM) of mefenamic acid (A) and 0.3 (mM) indomethacin (B). At CHM-GC electrode, oxidation of these drugs resulted in a typical electrocatalytic response. In the presence of these drugs, it was observed that the anodic current and the associated anodic charge increased drastically, while the cathodic current and the corresponding charge decreased.

Figures 5(A, A1) and 5(B, B1) presents the CVs of CHM-GC electrode in the presence of mefenamic acid (A) and indomethacin (B) recorded at the potential sweep rate of 2-200 and 10-500 mVs^{-1}, respectively. These indicate that mefenamic acid and indomethacin are oxidized in the anodic sweep and as mefenamic acid and indomethacin are not electro-active in the potential window, it seems that its oxidation is mediated by the surface high valence cobalt. The significant current in the reverse sweep indicates that the reaction of these drugs or its intermediates with cobalt hydroxide is/are probably the rate determining step of the process.[38,39]

Figure 6A and 6B show that upon increasing mefenamic acid and indomethacin concentration its irreversible oxidation develops in the region of the electrochemical formation of Co (IV). Thus, it is likely that the electro-generated Co (IV) species is the active moiety which efficiently speeds up the oxidation of drugs.[38,39] Any increase in the concentration of drugs causes a proportional almost linear enhancement of the anodic wave, Figure 6A and 6B. It is worth to emphasis that the anodic formation of Co (IV) seems to be an irreversible process. It is observed that in the presence of mefenamic acid and indomethacin the anodic current increases while the cathodic current decreases and the charges associated with the processes also behave accordingly to the extent of 18.71%, 23.44%, respectively.

On the basis of the reported results, the following mechanism can be proposed for the mediated oxidation processes. The redox transition of cobalt species:

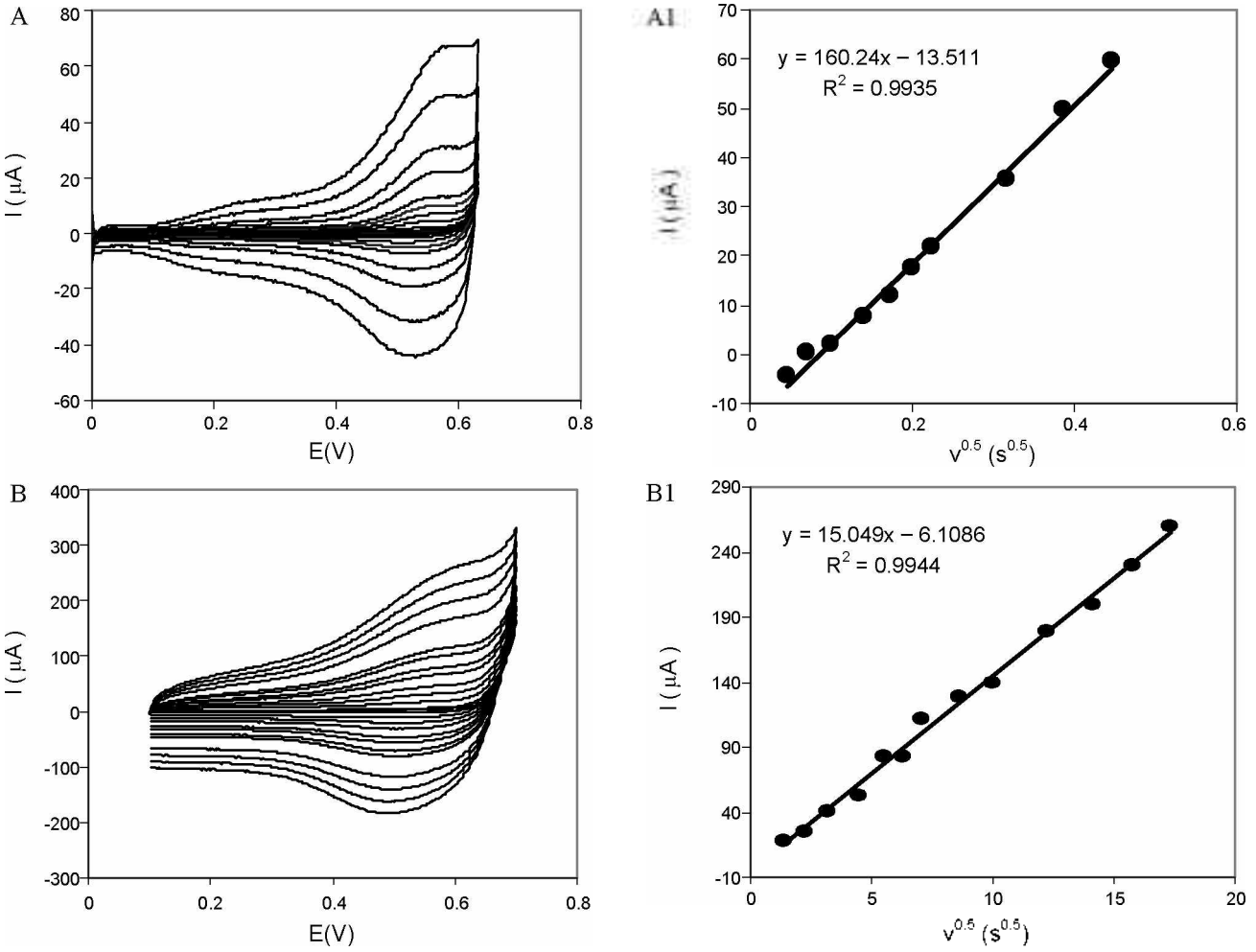


Figure 5. A: Cyclic voltammograms of the CHM-GC electrode in 100mM NaOH solution in the presence of mefenamic acid at various potential sweep rates of 2 ,5, 10, 20, 30, 40, 50, 100, 150, 200 mVs^{-1}. **A1**: dependence of anodic peak current on the square roots of potential sweep rate. **B**: Cyclic voltammograms of the CHM-GC electrode in 100mM NaOH solution in the presence of indomethacin various potential sweep rates of 2,5,10,20,30,40,50,100,150, 200, 300, 400, 500 mVs^{-1}. **B1**: dependence of anodic peak current on the square roots of potential sweep rate.

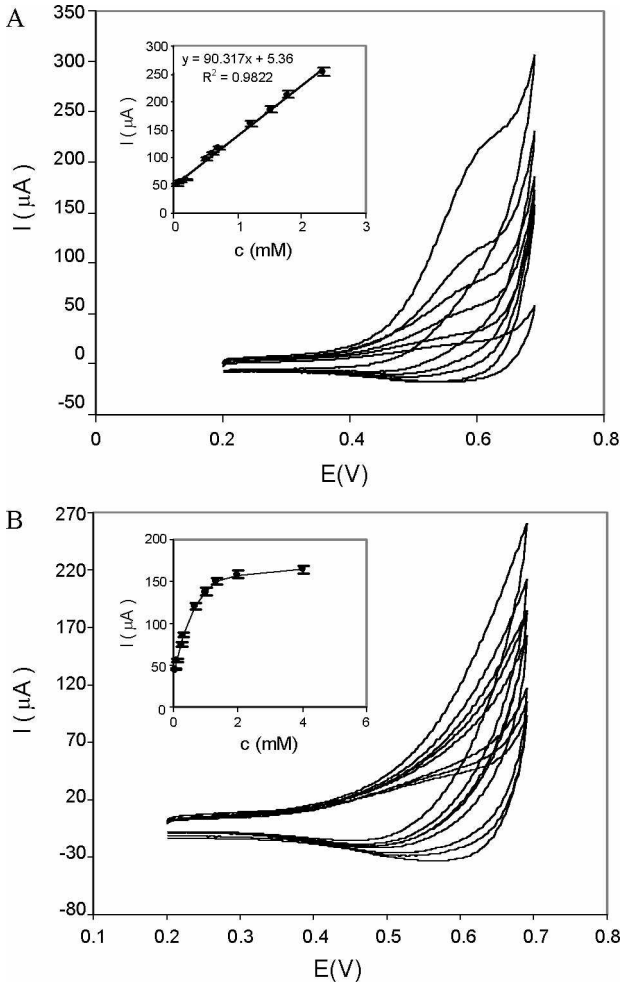


Figure 6. A: Cyclic voltammograms of CHM-GC electrode in 100 mM NaOH solution in the presence of different concentrations of mefenamic acid: 0.05 (a), 0.1 (b), 0.5 (c), 0.8 (d), 1.01 (e) and 2.30 mM (f), respectively. The potential sweep rate is 100 mV s^{-1}. Inset: dependency of the anodic current electro-oxidation on mefenamic acid concentration in the range of 0.01-2.33 mM. **B**: Cyclic voltammograms of CHM-GC electrode in 100mM NaOH solution in the presence of different concentrations of indomethacin: 0.01 (a), 0.05 (b), 0.1 (c),0.5 (d), 1 (d), 2 (e) and 2.3 mM (f) and respectively. Inset: dependency of the anodic current electro-oxidation on indomethacin concentration in the range of 0.01-4 mM. The potential sweep rate is 100 mV s^{-1}.

$$Co^{III} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Co^{II} + e \quad (2)$$

$$Co^{II} + Druge \xrightarrow{K_2(E)} intermediate + Co^{III} \quad (3)$$

Where the intermediate is further oxidized to the product through a similar electro-oxidation process:

$$Co^{II} + intermediate \xrightarrow{K_3(E)} Product + Co^{III} \quad (4)$$

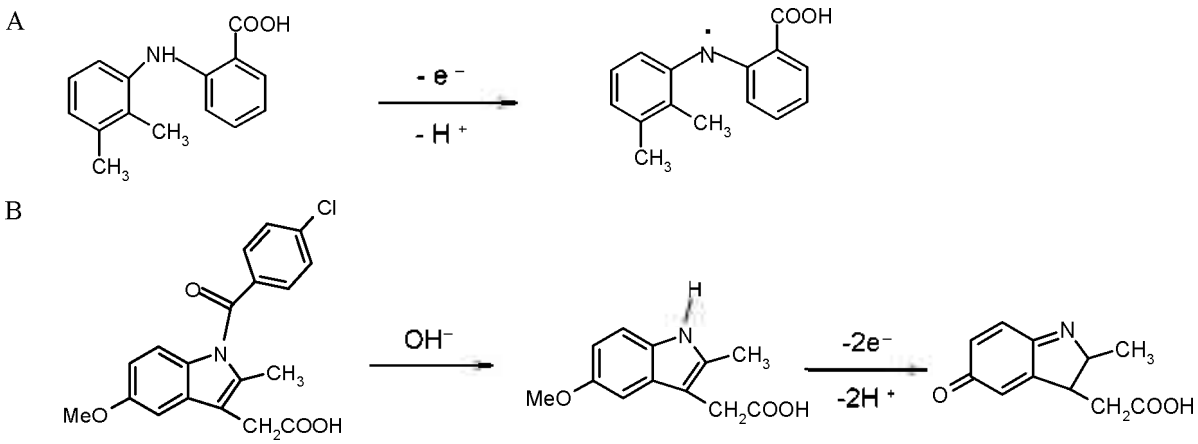
Our results revealed that the numbers of protons in the processes are equal to the number of the transferred electrons. As shown in Scheme 1, this conclusion is in accordance with the known electrochemical reactions of MEF, and IND.[40-41] As shown in Scheme 1 (A&B). MEF and IND can be oxidized *via* one and two electrons and one and two protons processes, respectively.

Chronoamperometry. Chronoamperometry, as well as cyclic voltammetry has been employed for the investigation of the processes occurring *via* E_rC_i mechanism.[42] The chronoamperograms of CHM-GC electrode in the absence (curve a) and presence of mefenamic acid (curves b-f) in 100 mM NaOH at the oxidation potential of 580 and 560 mV/SCE, are presented in Figure 7A. The plot of net current versus $t^{-0.5}$ which has been obtained by removing the background current by the point-by-point subtraction method gives a straight line, Figure 7B. This indicates that the transient current must be controlled by a diffusion process.[42] The transient current is due to catalytic oxidation of this drug and the current increases as the mefenamic acid concentration is raised. No significant cathodic current is observed when the electrolysis potential is stepped to 0 V/SCE indicating the irreversible nature of the oxidation of the drug.[43] Similar chronoamperograms were obtained for indomethacin.

The rate constants of the reactions of these drugs and their ensured intermediates with the redox sites of the CHM-GC electrode can be derived from the chronoamperograms according to:[40]

$$\frac{I_{catal}}{I_d} = \lambda^{1/2}\left[\pi^{1/2} erf(\lambda^{1/2}) + \frac{\exp(-\lambda)}{\lambda^{1/2}}\right] \quad (5)$$

where I_{catal} is the catalytic current in the presence of



Scheme 1. Oxidation mechanism of MEF (A) and IND (B).

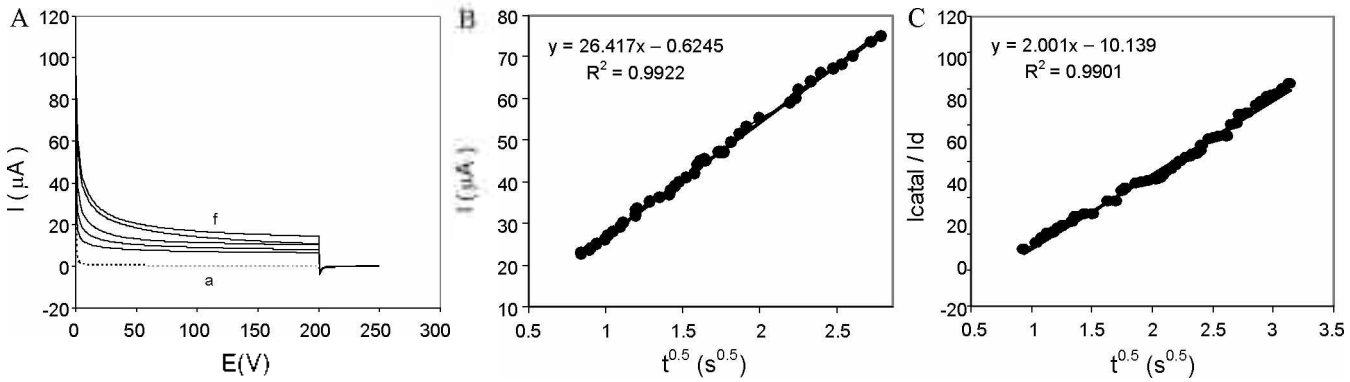


Figure 7. **A**: Double steps chronoamperograms of CHM-GC electrode in the absence (a) and the presence of 0.01 (b), 0.05 (c), and 0.1(d) 1 (e) and 2 mM (f) mefenamic acid in 100 mM NaOH solution. Potential steps were 600 mV and 200 mV, respectively. **B**: Dependency of transient current on $t^{-0.5}$. **C**: Dependence of I_{catal}/I_d on $t^{0.5}$ derived from the data of chronoamperograms of (a) and (e) in main panel.

mefenamic acid and indomethacin. I_d the limiting current in the absence of drugs $\lambda = kCt$ and (k, C and t are the catalytic rate constant, bulk concentration of drugs and the elapsed time, respectively) is the argument of the error function. For $\lambda >$ 1.5, erf ($\lambda^{0.5}$) almost equals unity and Eq. (5) reduces to:

$$\frac{I_{catal}}{I_d} = \lambda^{1/2}\pi^{1/2} = \pi^{1/2}(kCt)^{1/2} \tag{6}$$

From the slope of the I_{catal}/I_d plot the value of k at a given concentration of these drugs are derived. Figure 7C presents the graphs both in the absence and presence of mefenamic acid 1 mM concentration. The mean value of k in the concentration range of 0.01-2 mM and 0.01-1.15 mM were found to be 8.25×10^5 and 3.62×10^5 cm^3 mol^{-1} s^{-1} for mefenamic acid and indomethacin, respectively. It should be pointed out that k is either k_2 or k_3 whichever is smaller.

Steady state polarization. The rate laws for the reactions of 2 and 3 have the forms of:

$$v_1 = k_1\Gamma\theta_{III} - k_{-1}\Gamma\theta_{II'} \tag{7}$$

$$v_2 = k_2\Gamma\theta_{II'}C_m \tag{8}$$

Where Γ is the total number of adsorption sites per unit area of the electrode surface, θ's represents the fractional surface coverages of CHM-GC of different valence states and C_m is the bulk concentration of mefenamic acid and indomethacin. With only the 3 and 4 valence states of cobalt prevailing one has:

$$\theta_{III} + \theta_{II'} = 1 \tag{9}$$

And the rate of changes of their surface coverages as well as that of the intermediate compounds is:

$$\frac{d\theta_{III}}{dt} = -\frac{d\theta_{II'}}{dt} = -k_1\theta_{III} + k_{-1}\theta_{II'} + k_2\theta_{II'}C_m + k_3\theta_{II'}C_i \tag{10}$$

$$\frac{dc_i}{dt} = k_2\theta_{II'}C_m - k_3\theta_{II'}C_i \tag{11}$$

where C_i is the concentration of the intermediate. Assuming that the steady state dominates:

$$\frac{d\theta_{III}}{dt} = -\frac{d\theta_{II'}}{dt} = 0 \tag{12}$$

$$\frac{dC_i}{dt} = 0 \tag{13}$$

one arrives at the values if the coverages:

$$\theta_{III} = \left(\frac{k_{-1} + 2k_2C_m}{k_1 + k_{-1} + 2k_2C_m}\right) \tag{14}$$

$$\theta_{II'} = \left(\frac{k_1}{k_1 + k_{-1} + 2k_2C_m}\right) \tag{15}$$

and subsequently:

$$v_1 = \left(\frac{2k_1\Gamma k_2C_m}{k_1 + k_{-1} + 2k_2C_m}\right) \tag{16}$$

On the basis of this rate equation the faradic current will be:

$$i_f = \left(\frac{2FAk_1\Gamma k_2C_m}{k_1 + k_{-1} + 2k_2C_m}\right) \tag{17}$$

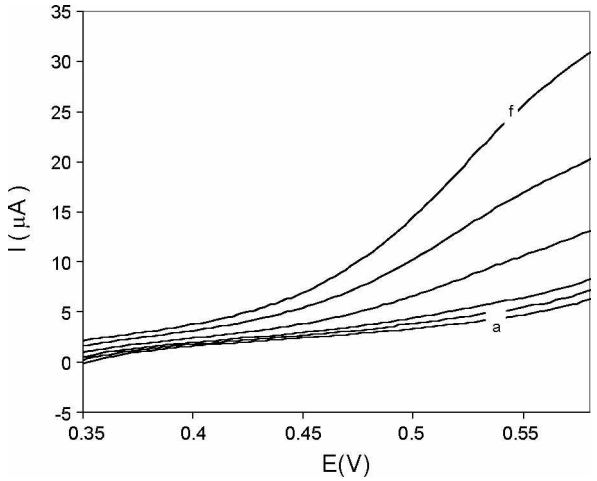


Figure 8. Typical pseudo-steady state polarization curves of CHM-GC electrode obtained in 0.01 (a), 0.05 (b), 0.1 (c) 0.5 (d), 1 (e), and 2 mM (f) mefenamic acid, respectively.

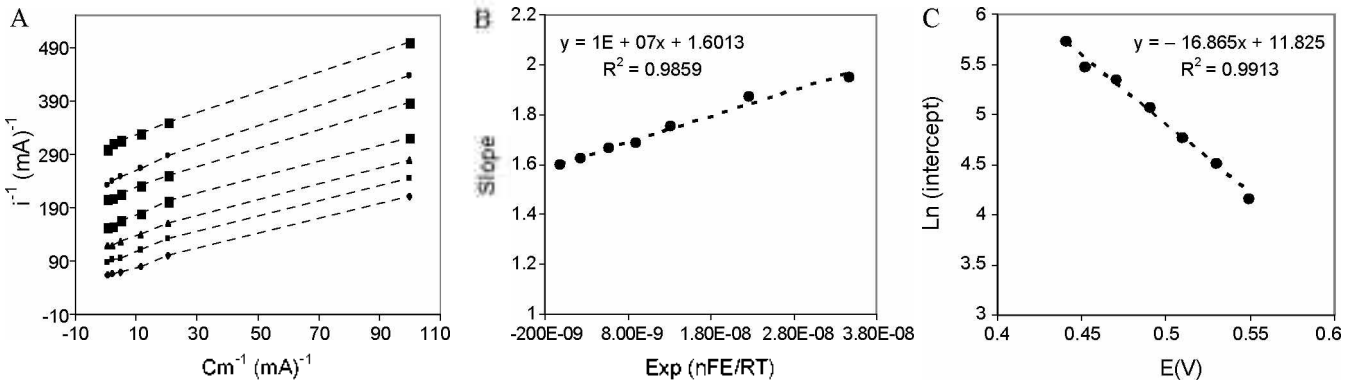


Figure 9. A: Plot of i^{-1} (from polarization curves in Fig. 8) against C_m^{-1} at various potentials: 440, 452, 471, 491, 510, 530, and 549 mV/ SCE as curves (a-g). **B**: Plot of the slopes (of curves in A) *vs.* Exp (-nFE/RT). **C**: Plot of the ln (intercepts) (of curves in A) *vs.* applied potential.

Table 1. Values of the $k_2\Gamma$, $k^o_1\Gamma$, $k^o_{-1}\Gamma$, α and b (Tafel slope) obtained from polarization curves.

Drugs	$k_2\Gamma$ ($cm\ s^{-1}$)	$k^o_1\Gamma$ ($mol\ s^{-1}\ cm^{-2}$)	$k^o_{-1}\Gamma$ ($mol\ s^{-1} cm^{-2}$)	α	b
Mefenamic acid	2.51×10^{-8}	6.06×10^{-10}	3.65×10^{-3}	0.44	56.30
Indomethacin	9.39×10^{-10}	5.21×10^{-9}	3.41×10^{1}	0.45	55.05

Where A is the surface area of the electrode and the rate constants k_1 and k_{-1} are obviously potential dependent and are of the forms

$$k_1(E) = k^0{}_1 \exp\left[\frac{\alpha nFE}{RT}\right] \quad (18)$$

$$k_{-1}(E) = k^0{}_{-1} \exp\left[\frac{(\alpha - 1)nFE}{RT}\right] \quad (19)$$

Where k^0 s are the chemical rate constants measured at E/SCE = 0 with a being the anodic transfer coefficient and other parameters have their usual meanings. Eq. (17) is well suited for the calculation of rate constants, the validity test of the kinetics, and mechanism of the oxidation process.

The pseudo-steady state polarization curves of the electrooxidation of mefenamic acid on CHM-GC electrode at a number of mefenamic acid concentrations are presented in Figure 8. The oxidation process was found to begin at nearly 400 mV/ SCE and to reach a plateau at 560 mV/ SCE, while the oxygen evolution starts at even higher potentials. In the course of reaction the coverage of Co (IV) increases and reaches a saturation (steady state) level and the oxidation current follows accordingly. At potentials as high as 600 mV/SCE the decomposition (oxidation) of solvent interferes and the plateau region becomes ill-defined. According to Eq. (18) the plots of the inverse of current against the inverse of mefenamic acid concentration should be linear:

$$i_f^{-1} = (FAk_1\Gamma)^{-1} + \left[\frac{k_1 + k_{-1}}{2FAk_1k_2\Gamma}\right] C_m^{-1} \quad (20)$$

Figure 9A presents the i^{-1} versus C_m^{-1} dependencies where straight lines at various potentials have been obtained. Both the intercepts and slopes of the straight lines appearing in this figure were potential dependent. The slopes are plotted against exp (-nFE/RT) with n = 1 and the graph is presented in Figure 9B. Using this graph along with Eq. (20) reveals that the rate constant of reaction 3, $k_2\Gamma$, and the ratio of k^o_{-1}/k^o_1 are 2.51×10^{-8} and 6.03×10^{6} cm s^{-1}, respectively. Figure 9C presents the variation of the intercepts of the lines in Figure 9A with the applied potential in a semi-log scale. Using this graph and Eq. (20) the magnitudes of $k^o_1\Gamma$ and the anodic transfer coefficient of 6.06×10^{-10} mol s^{-1} cm^{-2} and 0.44 have been obtained. From the above findings the value of $k^o_{-1}\Gamma$ was worked out to be 3.65×10^{-3} mol s^{-1} cm^{-2}. Similar pseudo-steady state polarization curves were collected for indomethacin.

The values of $k_2\Gamma$, $k^o_1\Gamma$, $k^o_{-1}\Gamma$, α and b (Tafel slope) obtained according to the method described in the above for these drugs were reported in Table1.

Conclusion

The cobalt hydroxide film was formed electrochemically in a regime of cyclic voltammetry on a glassy carbon electrode and checked for electrooxidation of mefenamic acid and indomethacin in alkaline media. The modified eletrode shows electrocatalytic oxidation of mefenamic acid and indomethacin at around 530 and 570 mV/ SCE. Using cyclic voltammetry, chronoamperometry techniques, steady-state polarization measurements, the kinetic parameters, such as charge transfer coefficient (α) and the catalytical reaction rate constant (k) for oxidation of mefenamic acid and indomethacin were determined. The kinetics of the reaction based on the above mechanism has been developed and the magnitudes of the rate constants, as well as, anodic transfer coefficient of the electrooxidation reaction have been obtained.

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