Turkish Journal of Chemistry

Volume 34 | Number 1 Article 4

1-1-2010

# Electro-oxidation of some non-steroidal anti-inflammatory drugs on an alumina nanoparticle-modified glassy carbon electrode

MAHLA TABESHNIA

HOSSEIN HELI

ALI JABBARI

ALI A. MOOSAVI-MOVAHEDI

Turk J Chem
34 (2010) , 35 – 45.

doi:10.3906/kim-0810-9

# Electro-oxidation of some non-steroidal anti-inflammatory drugs on an alumina nanoparticle-modified glassy carbon electrode

**Mahla TABESHNIA[3], Hossein HELI[1,2], Ali JABBARI[3,*]**
**Ali A. MOOSAVI-MOVAHEDI[1]**
[1]*Institute of Biochemistry and Biophysics, University of Tehran, Tehran-IRAN*
[2]*Department of Chemistry, Razi University, Kermanshah-IRAN*
[3]*Department of Chemistry, Faculty of Science, K. N. Toosi University of Technology, P. O. Box: 16315-1618, Tehran-IRAN*
*e-mail: jabbari@kntu.ac.ir*

Received 07.10.2008

The electro-oxidation of mefenamic acid, diclofenac, and indomethacin on glassy carbon and alumina nanoparticle-modified glassy carbon electrodes in a phosphate buffer solution at physiological pH was studied. The techniques of cyclic voltammetry, chronoamperometry, impedance spectroscopy, and steady state polarization measurements were applied. The drugs were irreversibly oxidized on bath electrodes via an anodic peak and the process was controlled by diffusion in the bulk of solution. Alumina nanoparticles increased the oxidation current, and lowered the peak and onset potentials. As such, alumina nanoparticles had an electrocatalytic effect, both kinetically and thermodynamically. The kinetic parameters of heterogeneous electron transfer and diffusion coefficients of the drugs are reported.

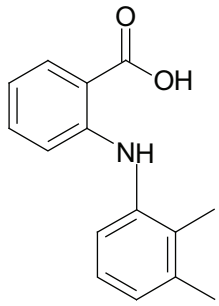
**Key Words:** Modified electrode; alumina nanoparticle; electrocatalysis; mefenamic acid, diclofenac, indomethacin

## Introduction

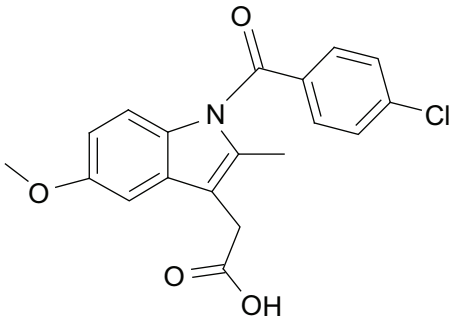
Mefenamic acid (2-[(2,3-dimethylphenyl) amino] benzoic acid, Scheme 1), indomethacin (1-(p-chlorobenzoyl)-5-methoxy-2-methyl-3-indolylacetic acid, Scheme 2), and diclofenac ([2-[(2,6-dichlorophenyl)amino]phenyl]acetic

*Corresponding author

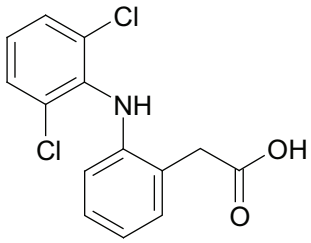
acid, Scheme 3) are important non-steroidal anti-inflammatory drugs (NSAIDs) used to treat several pathologies. NSAIDs have been widely used due to their anti-inflammatory and analgesic properties. The indications for NSAID use are broadening—from rheumatic diseases and various pain states, such as cancer pain, and biliary and colic pain—to possibly include Alzheimer's disease and colon cancer prevention.[1] Although all NSAIDs are weak organic acids, they are grouped into several classes based on their chemical structure. Although this chemical diversity yields a broad range of pharmacokinetic characteristics,[2] they have some general properties in common. NSAIDs have been shown to induce various forms of adverse drug reactions, including adverse gastrointestinal effects,[1] renal dysfunction and nephrotoxicity,[1] liver damage,[1] adverse neurological effects,[1] and rhabdomyolysis.[3]




**Scheme 1.** The chemical structure of mefenamic acid.




**Scheme 2.** The chemical structure of indomethacin.




**Scheme 3.** The chemical structure of diclofenac.

Drug analysis has great impact on public health. Despite their widespread application and use, little work has been reported on the electrochemical behavior of NSAIDs and the related sensing devices.[4] Electrochemical techniques include the determination of a drug's electrode mechanism.[5–13] The redox properties of drugs can provide insight into their metabolic fate, in vivo redox processes, and pharmacological activity.[14]

Modification of electrode surfaces has played an important role in the study of electron transfer kinetics and electrocatalytic reactions.[5,6,15] It has involved the formation of an electrocatalytic system in which redox species are capable of undergoing a rapid and reversible electrode reaction, reducing the over-potential required for either the oxidation or reduction of compounds

Nanostructured materials have attracted much interest from researchers due to the unique size-dependent properties[16,17] related to their small particle dimensions and size quantization effects.[18] Nanostructured materials have superior functional properties useful for a wide range of studies and applications, including catalysis, electrocatalysis, photonic devices, and microelectronics.[19]

Many studies have been performed based on nanoparticle-modified surfaces as chemical and biochemical tools in mechanistic studies and the determination of vast biologically important compounds; for example, gold nanoparticles for gene analysis,[20] platinum nanoparticles for determination of $H_2O_2$,[21] and carbon nanotubes and cobalt oxide nanoparticles for analysis of some drugs.[5,7] Alumina nanoparticle-modified electrodes exhibit attractive properties for electrocatalytic reactions.[22–25]

Building on our recent research on the electrocatalytic oxidation of some organics and drugs on modified surfaces,[5,7–10,15] in the present study the electrocatalytic oxidation of mefenamic acid, diclofenac, and indomethacin on an alumina nanoparticle-modified glassy carbon electrode (ANMGC) was investigated.

## Experimental section

All chemicals used were obtained from Merck (Darmstadt, Germany), were of analytical grade, and were used without further purification. All solutions were prepared with doubly distilled water. The drugs involved were obtained as a gift from the Center of Quality Control of Drugs, Tehran, Iran. Standard solutions of authentic drugs were prepared by dissolving an accurate mass of each bulk drug in an appropriate volume of 100 mM phosphate buffer solution (PBS, which was also used as the running electrolyte), and then storing 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.

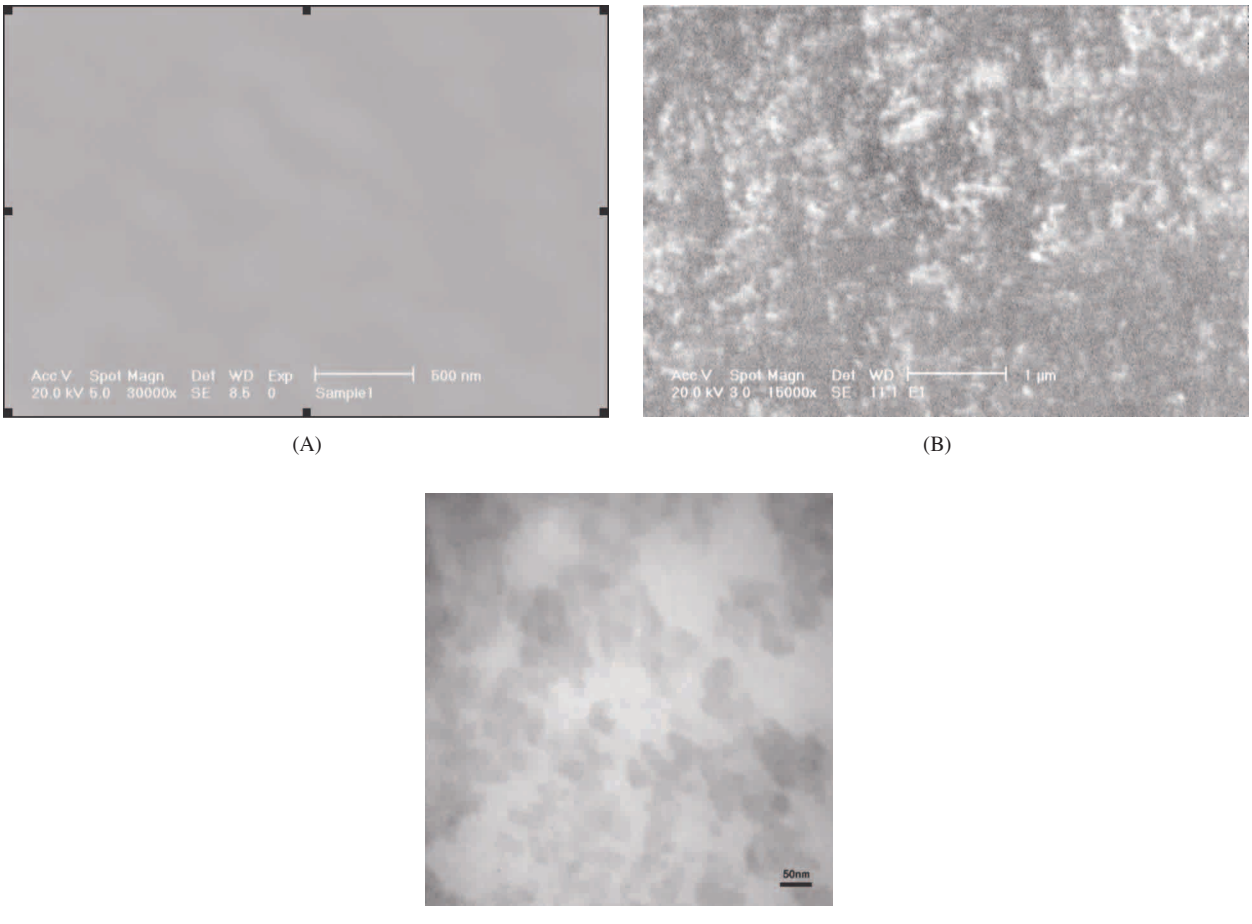
Electrochemical studies were carried out in a glass cell incorporating a 3-electrode configuration, powered by an AUTOLAB PGSTAT30 electrochemical analyzer equipped with FRA2 boards (Eco Chemie, Utrecht, The Netherlands). CV data were recorded in the analogue mode, with a fast analogue scan generator (SCANGEN) in combination with a fast AD converter (ADC750). For impedance measurements, a frequency range of 100 kHz to 25 MHz was employed, with AC voltage amplitude of 10 mV and an equilibrium time of 5 s. The system was run on a PC using FRA and GPES 4.9 software. The kinetic parameters of the electro-oxidation processes were also calculated using the fitting tool in GPES. An Ag/AgCl, 3M KCl (from Metrohm), and a platinum plate (from Azar Electrode Co., Iran) were used as the reference and counter electrodes, respectively. Additionally, a glassy carbon (GC) disk (from Azar Electrode Co., Iran) with a geometric surface area of 0.031 $cm^2$ or an alumina nanoparticle-modified GC disk with a real surface area of 0.052 $cm^2$ (obtained by chronoamperometry) was used as the working electrode. The surface of the GC electrode was polished successively with alumina powder on a polishing micro-cloth, rinsed thoroughly with distilled water, placed in $HNO_3$ (1:1), and then ultrasonicated in a water/acetone mixture for 5 min. The electrode prepared by this procedure will be referred to as the bare GC electrode. In order to modify the GC surface we placed 30 $\mu$L of alumina suspension in

water on the surface, allowed it to dry, and then the surface was rinsed thoroughly with water.

Surface morphological studies were carried out using scanning electron microscopy (SEM), (Philips model X-30). Transmission electron microscopy (TEM) was performed using a Zeiss model CEM 902A with an accelerating voltage of 80 kV. Samples were prepared by placing a drop of the particles, dispersed in distilled water, on a carbon-covered nickel grid and evaporating the solvent.

## Results and discussion

In order to investigate the surface morphology of alumina nanoparticles (ANs) they were examined using SEM and TEM. SEM micrographs of the GC (A) and ANMGC (B) electrode surfaces are shown in Figure 1. In addition, Figure 1C shows the transmission electron micrographs of ANs. Nearly spherical ANs $\leq$ 50 nm in diameter were homogeneously dispersed on the GC surface.




(A) (B)

(C)

**Figure 1.** SEM images of GC (A) and ANMGC (B) electrode surfaces, and a TEM image of ANs (C).

Figure 2 represents a typical cyclic voltammogram of 1.0 mM mefenamic acid (a), 1.0 mM indomethacin (b), and 1.0 mM diclofenac (c) in PBS using a GC electrode in the potential range of 300-800 mV, in which a

potential sweep rate of 100 mV $s^{-1}$ was employed. In the course of the anodic sweep, the drugs were oxidized via an anodic peak located at 636, 537, and 652 mV for mefenamic acid, indomethacin, and diclofenac, respectively. For the reverse one, however, no marked corresponding cathodic peak was observed. This indicates that the drugs oxidized irreversibly on the GC surface. Considering the chemical structures of the drugs, the reactions shown in Scheme 4 can be proposed for electro-oxidation reactions.[26,27]

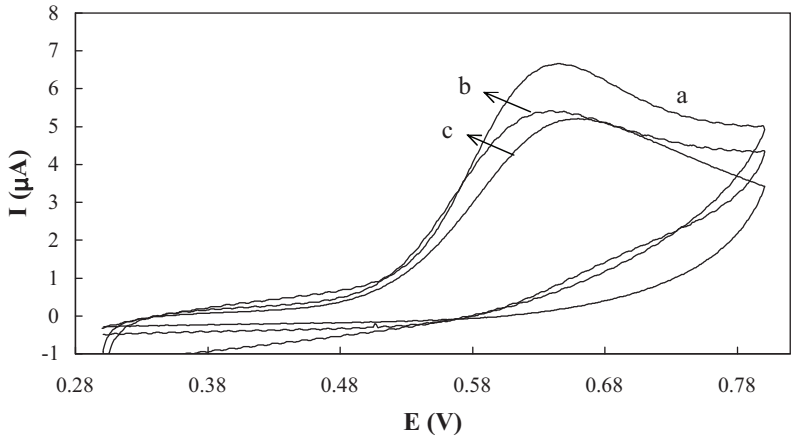



**Figure 2.** Cyclic voltammograms of the GC electrode in the presence of 1.0 mM mefenamic acid (a), 1.0 mM indomethacin (b), and 1.0 mM diclofenac (c) in PBS. The potential sweep rate was 50 mV $s^{-1}$.

Cyclic voltammograms of 1.0 mM mefenamic acid (a), 1.0 mM indomethacin (b), and 1.0 mM diclofenac (c) in PBS recorded using the ANMGC electrode are shown in Figure 3. In all cases the onset and peak potentials of the oxidation processes were shifted in a negative direction, as compared to those of the GC electrode. Moreover, the anodic peak currents of the drugs increased. Decreasing the onset and peak potentials of the electro-oxidation process using the ANMGC electrode indicates that ANs caused the process to occur at a thermodynamically favorable potential, with lower energy. Furthermore, the enhancement in the peak currents implies that the rates of the processes were increased by ANs; therefore, ANs promoted the electro-oxidation of the drugs, both thermodynamically and kinetically, and ANs catalyzed the processes.

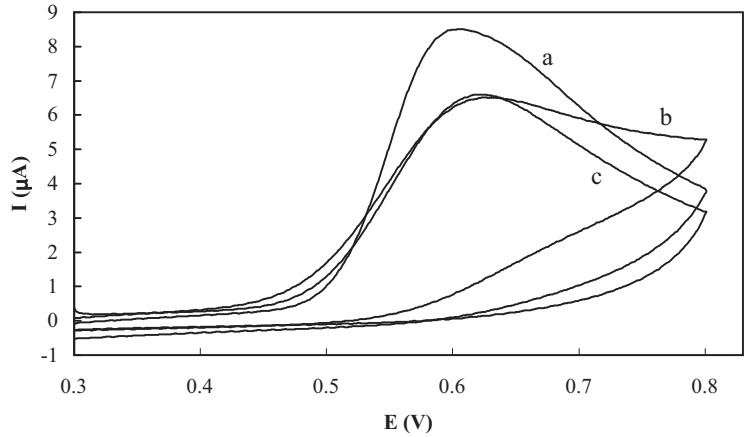
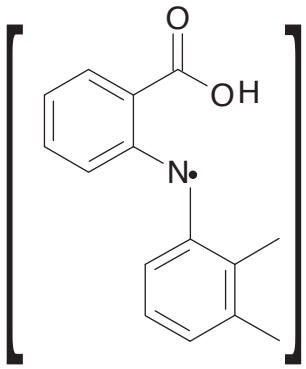
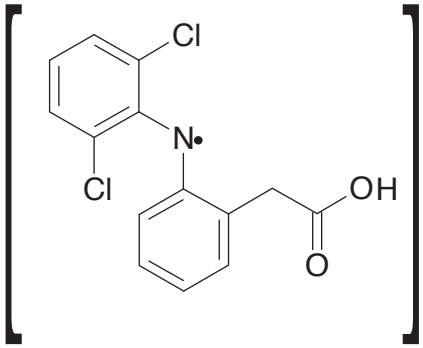


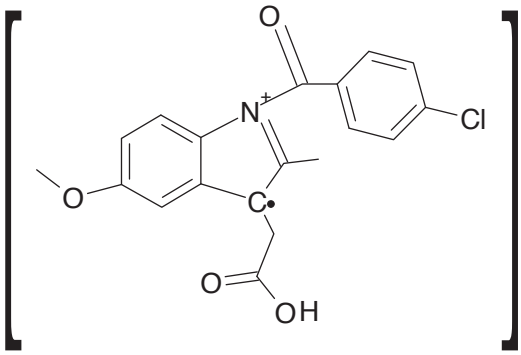

**Figure 3.** Cyclic voltammograms of the ANMGC electrode in the presence of 1.0 mM mefenamic acid (a), 1.0 mM indomethacin (b), and 1.0 mM diclofenac (c) in PBS. The potential sweep rate was 50 mV $s^{-1}$.




Mefenamic Acid




Diclofenac




Indomethacin

**Scheme 4.** The electro-oxidation reaction of the drugs.

Although alumina itself is a non-conductor, the adsorbed species are apparently electro-reactive. In the case of alumina, it appears that any oxidative process involving adsorbed intermediate(s) and/or the loss of a proton in the electron-transfer process can be catalyzed. The alumina is somewhat of an "adsorbing base",

which can catalyze the oxidation, and, furthermore, any oxidation process involving the loss of a proton in the electron transfer process can be catalyzed. The variation in acid-base properties of alumina in effecting chromatographic separations is well known.[23]

The values of the kinetic parameters (the standard rate constant, $k^0$, and the electron transfer coefficient, $\alpha$) related to the electro-oxidation process can be obtained by using the fitting option in the GPES program. Using the fitting method, the values of $k^0$ and $\alpha$ were obtained, and are reported in the Table. It can be deduced that the rate of the electro-oxidation process increase using the modified surface. This also confirms the electrocatalytic nature of ANs.

**Table.** The electron transfer coefficients ($\alpha$) obtained from Tafel plots, the standard rate constants ($k^0$) obtained from cyclic voltammetry, the diffusion coefficients (D) obtained from chronoamperometry, and peak currents and potentials obtained from cyclic voltammetry for mefenamic acid, indomethacin, and diclofenac on the bare GC (indicated with a subscript G) and the ANMGC (indicated with a subscript M).

| | $\alpha_G$ | $\alpha_M$ | D ($cm^2s^{-1}$) | $k^0_G$ ($cm^3$ $mol^{-1}$ $s^{-1}$) | $k^0_M$ ($cm^3$ $mol^{-1}$ $s^{-1}$) | $I_{p,G}$ ($\mu$A) | $I_{p,M}$ ($\mu$A) | $E_{p,G}$ (mV) | $E_{p,M}$ (mV) |
|---|---|---|---|---|---|---|---|---|---|
| Mefenamic acid | 0.50 | 0.74 | $3.1 \times 10^{-6}$ | $3.2 \times 10^{-9}$ | $1.0 \times 10^{-7}$ | 6.63 | 8.51 | 648 | 600 |
| Indomethacin | 0.56 | 0.56 | $3.1 \times 10^{-6}$ | $1.0 \times 10^{-4}$ | $1.0 \times 10^{-3}$ | 5.39 | 6.56 | 644 | 625 |
| Diclofenac | 0.58 | 0.53 | $5.1 \times 10^{-6}$ | $3.1 \times 10^{-4}$ | $3.1 \times 10^{-3}$ | 5.19 | 6.59 | 664 | 620 |

Typical pseudo-steady state current-potential curves for the electro-oxidation of the drugs were recorded (data not shown). The electron transfer coefficient ($\alpha$) can also be found by plotting E vs. log I, and the slope of this plot is equal to $2.3RT/\alpha F$. The values of $\alpha$ for the electro-oxidation process, using both electrodes, were obtained and are shown in the Table.

Double-step chronoamperograms were recorded by setting the working electrode potentials to the desired values and were used to measure the diffusion coefficients of the drugs. Figure 4 shows double-step chronoamperograms for GC (b) and ANMGC (a) electrodes in the presence of 1.0 mM mefenamic acid. During the first potential step, the transient current was higher using the modified electrode, due to the electrocatalytic effect of ANs. Plotting the net currents, with respect to the minus square roots of time, presents linear dependencies for both electrodes (insets A and B); therefore, a diffusion-controlled process dominated during the electro-oxidation process using both electrodes. By using the slope of the line the diffusion coefficient of mefenamic acid on the bare electrode can be obtained according to the Cottrell equation:[28]

$$I = nFAD^{1/2}C\pi^{-1/2}t^{-1/2} \tag{7}$$

where D is the diffusion coefficient and C* is the bulk concentration of the electro-reactive species. The mean value of the diffusion coefficient obtained for this drug, according to this method, is reported in the Table. Diffusion of an electro-reactive species in a Cottrellian manner occurred in the bulk of the solution; therefore, it did not depend on the morphology or nature of the electrode surface. The difference between the slopes of the lines represented in Figure 4 (insets A and B) could be related to the difference between the real surface areas of the bare and the modified electrodes. If we use the obtained value for the diffusion coefficient and the Cottrell equation, the real surface area of ANMGC is 0.086 $cm^2$. Similar chronoamperograms were recorded for

indomethacin and diclofenac (data not shown), and the diffusion coefficients for indomethacin and diclofenac are reported in the Table.

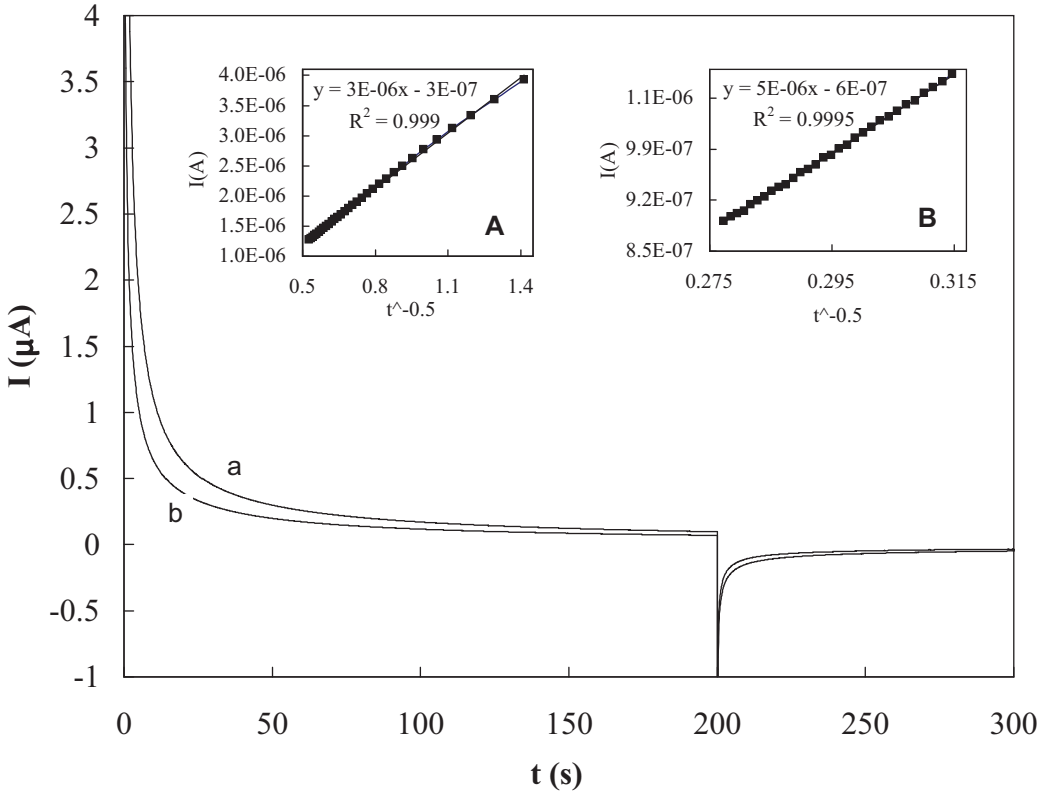



**Figure 4.** Double-step chronoamperograms of the GC (b) and ANMGC electrodes (a) in PBS solution containing 1.0 mM of mefenamic acid. Inset A: Dependency of the transient current on $t^{-0.5}$ for the GC electrode. Inset B: Dependency of the transient current on $t^{-0.5}$ for the ANMGC electrode.

Figure 5 shows Nyquist diagrams of PBS containing 1.0 mM mefenamic acid recorded using the GC (a) and ANMGC (b) electrodes at 631 mV as the DC-offset. Both diagrams represent a relatively depressed semicircle at high frequencies and a line with a slope near unity at low frequencies. This implies that the electro-oxidation process occurred in a mixed regime of charge and mass transfers. The electrical equivalent circuit compatible with these Nyquist diagrams is shown in the inset of Figure 5. In this equivalent circuit $R_s$, $CPE_{dl}$, $R_{ct}$, and W represent solution resistance, a constant phase element indicating double layer capacitance, charge transfer resistance, and Warburg impedance, respectively. A constant phase element was used instead of pure capacitance due to the depression of the high frequency semicircle and its relationship to the surface inhomogeneities located on the working electrode surface.[28] The line that appeared at low frequencies implies that the diffusion of the electro-reactive species occurred in the bulk of solution and that is a Warburg-type impedance. This impedance appeared in the Nyquist diagrams for both GC and ANMGC electrodes; however, the semicircle that appeared in the high frequencies, which is related to the heterogeneous charge transfer process, was smaller in diameter in the case of the ANMGC electrode. This indicates, in fact, that the charge transfer resistance for the electro-oxidation process on the surface of the ANMGC electrode was less than that

of the bare electrode. Lowering the charge transfer is due to raising the rate of the electrode process and increasing the heterogeneous charge transfer rate. Similar Nyquist diagrams were recorded for indomethacin and diclofenac, and very similar results were obtained (data not shown). These results were confirmed by those obtained from cyclic voltammetry studies; both techniques imply that ANs catalyzed the reactions.

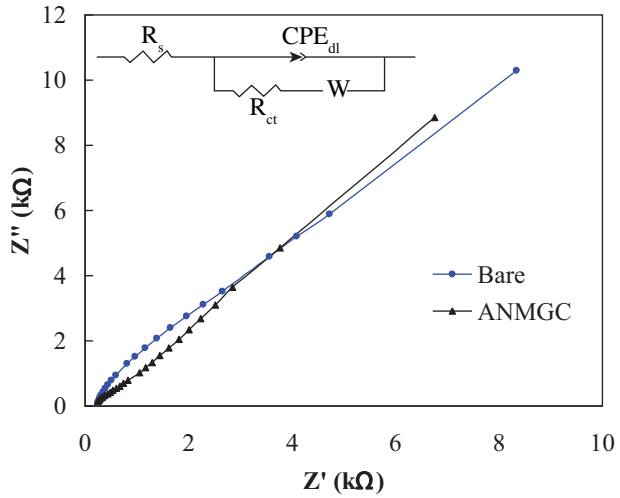



**Figure 5.** Nyquist diagrams of PBS containing 1.0 mM of mefenamic acid recorded using bare (a) and ANMGC (b) electrodes at 631 mV as the DC-offset.

It is well known that the differential pulse voltammetric signals depend on the rate of heterogeneous electron transfer. In PBS, mefenamic acid gave a differential pulse peak at 526 mV on the modified electrode (a1) and at 565 mV on the GC electrode (a2) (Figure 6). A shift of 39 mV in the negative direction appeared. Moreover, the peak current increased 1.2-fold quantitatively using the modified electrode. This indicates that the detection sensitivity is greatly increased for mefenamic acid on the modified electrode surface. In Figure 6 similar differential pulse voltammograms are also shown for indomethacin (b1, b2) and diclofenac (c1, c2) using the bare electrode.

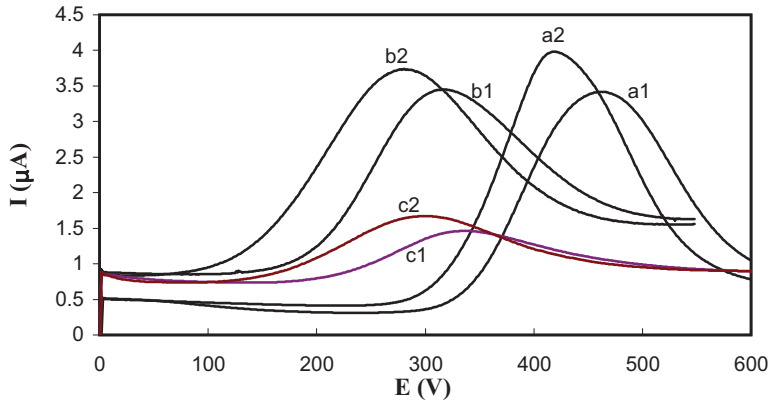



**Figure 6.** Differential pulse voltammograms for ANMGC (a1, b1, c1) and bare GC (a2, b2, c2) electrodes in PBS in the presence of 1.0 mM of mefenamic acid (a), 1.0 mM of indomethacin (b), and 1.0 mM of diclofenac (c).

According to the results represented above, it is clearly deduced that the electro-oxidation of the drugs was catalyzed by ANs. Although the peak current enhancement can be attributed to the real surface area increment, at the same time the potential of the electro-oxidation process was lowered. As such, the catalytic effect of ANs was not only related to the surface increment effect, because the surface can affect only the oxidation current. Metal oxide nanoparticles such as ANs exhibit different catalyzing performances due to the presence of different surface states. The mechanism of catalysis can be interpreted using the thin polymetric-coated electrode model.[29] A thin porous layer of carbon and ANs intimately intermixed adheres to the GC surface. ANs protrude from this layer and can be partially covered by carbon, which results in the double capacitance increase. In solution, polymer is swollen by the solvent, thereby allowing ions and/or electro-reactive species to penetrate. At the same time, the area of conduct of the porous carbon-ANs layer increases because of carbon, which results in current enhancement. Moreover, it has been reported that the electro-oxidation processes involving loss of a proton can be catalyzed by ANs, which is somewhat of a base.[23,25]

## Conclusion

A modified glassy carbon electrode with nanoparticles of aluminum oxide was prepared. It represented high electrocatalytic activity toward the oxidation of some anti-inflammatory drugs. By using ANs the rate of the oxidation process was increased.

## Acknowledgments

The financial support of the Iran National Science Foundation (INSF) is gratefully acknowledged.

### References

1. Day, R.; Quinn, D.; Williams, K.; Handel, M.; Brooks, P.; *Connective Tissue and Bone Disorders*, In *Clinical Pharmacology,* Carruthers, S. G.; Hoffmann, B. B.; Melmon, K L.; Nierenberg, D. W. McGraw-Hill, New York, 2000, p. 645.
2. Frust, D. E.; Munster, T. *Nonsteroidal Anti-Inflammatory Drugs, Disease-Modifying Antirheumatic Drugs, Nonopioid Analgesics, and Drugs used in Gout*, In *Basic and Clinical Pharmacology,* 8th ed, New York, McGraw-Hill, 2000, p. 596.
3. Leventhal, L. J.; Kuritsky, L.; Ginsburg, R.; Bomalaski, J. S. *Am. J. Emerg. Med.* **1989**, *7*, 409-410.
4. Liu, L.; Song, J. *Anal. Biochem.* **2006**, *354*, 22-27.
5. Yadegari, H.; Jabbari, A.; Heli, H.; Moosavi-Movahedi, A. A.; Karimian, K.; Khodadadi, A. *Electrochim. Acta* **2007**, *53*, 2907-2916.
6. Majdi, S.; Jabbari, A.; Heli, H.; Yadegari. H.; Moosavi- Movahedi, A. A.; Haghgoo, S. *J. Solid State Electrochem.* **2009**, *13*, 407-416.
7. Houshmand, M.; Jabbari, A.; Heli, H.; Hajjizadeh, M.; Moosavi-Movahedi, A. A. *J. Solid State Electrochem.* **2008**, *12*, 1117-1128.

8. Hajjizadeh, M.; Jabbari, A.; Heli, H.; Moosavi-Movahedi, A. A.; Haghgoo, S. *Electrochi. Acta* **2007**, *53*, 1766-1774.
9. Hajjizadeh, M.; Jabbari, A.; Heli, H.; Moosavi-Movahedi, A. A.; Shafiee, A.; Karimian, K. *Anal. Biochem.* **2007**, *373*, 337-348.
10. Majdi, S.; Jabbari, A.; Heli, H. *J. Solid State Electrochem*, **2007**, *11*, 601-607.
11. Yadegari, H; Jabbari, A.; Heli, H; Moosavi-Movahedi, A.A.; Karimian, K. *Chem. Anal. (Warsaw)*, **2008**, *53*, 5-16.
12. Hajjizadeh, M; Jabbari, A.; Heli, H; Moosavi-Movahedi, A.A. *Chem. Anal. (Warsaw)*, **2008**, *53*, 429-444.
13. Yadegari, H; Jabbari, A.; Heli, H; Moosavi-Movahedi, A. A; Majdi, S. *J. Braz. Chem. Soc.* **2008**, *19*, 1017-1022.
14. Ozkan, S. A.; Uslu, B.; Aboul-Enein, H. Y. *Crit. Rev. Anal. Chem.* **2003**, *33*, 155-181.
15. Majdi, S.; Jabbari, A.; Heli, H.; Moosavi-Movahedi, A. A. *Electrochim. Acta* **2007**, *52*, 4622-4629.
16. Zhang, Q-L.; Du, L-C.; Weng, Y-X.; Wang, L.; Chen, H-Y.; Li, J-Q. *J. Phys. Chem. B* **2004**, *108*, 15077-15083.
17. Heli, H; Hajjizadeh, M; Jabbari, A.; Moosavi-Movahedi, *Anal. Biochem.* **2009**, *388*, 81-90.
18. Cahn, R. W. *Nanostruct. Mater.* **1997**, *8*, 377-379.
19. (a) Whitney, T. M.; Jiang, J. S.; Searson, P. C. ; Chien, C. L. *Science* **1993**, *261*, 1316-1319. (b) Thurn-Albrecht, T.; Schotter, J.; Kastle, C. A.; Emley, N.; Shibauchi, T.; Krusin-Elbaum, L.; Guarini, K.; Black, C. T.; Tuominen, M. T.; Russell, T. P. *Science* **2000**, *290*, 2126-2129. (c) Heli, H; Hajjizadeh, M; Jabbari, A.; Moosavi-Movahedi, *Biosens. Bioelectron.* **2009**, *24*, 2328-2333.
20. Wang, J.; Li, J. H.; Baca, A. J.; Hu, J. B.; Zhou, F. M.; Yan, W.; Pang, D. W. *Anal. Chem.* **2003**, *75*, 3941-3945.
21. Sabahudin, H.; Liu, Y. L.; Keith, B. M.; John, H. T. L. *Anal.Chem.***2004**, *76*, 1083-1088.
22. Qiong, H.; Shuai, Y.; Cuie, C.; Shengshui, H. *Mater. Sci. Engin. C* **2003**, *23*, 621-625.
23. Zak, J.; Kuwana, T. *J. Am. Chem. Soc* **1982**, *104*, 5514-5515.
24. Yu, Z-Y.; Kong, D-S.; Wu, S-X.; Liu, T.; Wang, H-Q. *Indian J. Chem,* **2004**, *43A*, 2340-2342.
25. Kang, J.; Li, Z.; Lu, X.; Wang, Y. *Electrochim. Acta* **2004**, *50*, 19-26.
26. Li, L.; Junfeng, S. *Anal. Biochem.* **2006**, *354*, 22-27.
27. Lund, H.; Hammerich, O. *Organic Electrochemistry*, 4th End, Marcel Dekker Inc., New York, 2001, p. 564.
28. Bard, A. J.; Faulkner, L R. *Electrochemical Methods*, Wiley, New York, 2001, p. 163.
29. Dong, S. J.; Kuwana, T. *J. Electrochem. Soc,* **1984**, *131*, 813-819.