

Exploring the Theoretical and Electrochemical Attributes of Paracetamol Drug

Reza Safari¹ , Saeedeh Porhadi²  and Hasan Zandi³ 

1. Corresponding author, Department of Chemistry, Faculty of Science, University of Qom. Qom, Iran. Email: r.safari@qom.ac.ir

2. Department of Chemistry, Faculty of Science, University of Qom. Qom, Iran. Email: S.Porhadi1997@gmail.com

3. Department of Chemistry, Faculty of Science, University of Qom. Qom, Iran. Email: h.zandi@qom.ac.ir

Article Info

Article type:

Research Article

Article history:

Received 24 Jul 2024

Received in revised form 15 Sep 2024

Accepted 2 Nov 2024

Published online 25 Dec 2024

Keywords:

electrochemistry, computational chemistry, quantum mechanics, paracetamol, Graphene structures, acetaminophen.

ABSTRACT

Paracetamol is a widely used analgesic with high efficacy and minimal side effects, making it a preferred choice for patients with stomach ulcers or internal bleeding. This study investigates the electrooxidation of paracetamol using advanced electrochemical techniques, including cyclic voltammetry (CV), chronoamperometry (CA), and electrochemical impedance spectroscopy (EIS). Key parameters were optimized to enhance oxidation current, lower oxidation potential, and mitigate interference from competing species. Voltammetric analysis demonstrated that paracetamol significantly influences electrochemical responses, particularly on graphene-based electrodes, highlighting its strong redox activity. Complementary quantum chemical analyses—density functional theory (DFT) and quantum theory of atoms in molecules (QTAIM)—were employed to elucidate paracetamol's electronic and vibrational properties. Furthermore, the effects of an external electric field on intramolecular charge and energy transfer were examined to assess its potential for targeted drug delivery. Molecular simulations revealed that the electronic and vibrational behavior of paracetamol is highly sensitive to the magnitude and orientation of the applied field. These findings provide deeper insights into paracetamol's redox mechanisms and its interactions under electrochemical and field-induced conditions, paving the way for optimized drug formulations and delivery systems.

Cite this article: Safari, R. & et al, (2024). Exploring the theoretical and electrochemical attributes of paracetamol drug, *Advances in Energy and Materials Research*, 1 (4), 35-42. <https://doi.org/10.22091/jaem.2024.10349.1009>

© The Author(s).

DOI: 10.22091/jaem.2024.10349.1009

Publisher: University of Qom.

1. Introduction

The widespread integration of nano compounds into diverse aspects of daily life underscores their increasing relevance. Particularly, nano compounds have garnered substantial attention in medical applications, serving as carriers for therapeutic agents. This study explores the utilization of nano compounds as a drug carrier system with a focus on the vital pharmaceutical compound, paracetamol.

Recognizing the significance of paracetamol, the research delves into an extensive investigation of its structural, electronic, vibrational, and electrochemical properties. Acetaminophen, chemically represented as $C_8H_9NO_2$, stands as a prominent analgesic and antipyretic drug widely employed in treating various pains, including headaches, muscle pain, back pain, and toothaches.

As an over-the-counter analgesic and antipyretic, paracetamol plays a crucial role in relieving pain, forming a primary component in numerous cold and flu remedies. Furthermore, when combined with narcotic analgesics, it proves valuable in managing postoperative pain more effectively. The onset of the drug's effect occurs approximately 11 minutes after oral intake. Notably, it is important to note that while acetaminophen is effective for pain relief, it has only a negligible effect on inflammation [1].

Paracetamol, introduced by von Mering in 1893, gained commercial presence in the United States in 1950 and Australia in 1956. Despite concerns about over-the-counter pain reliever poisoning in the 1960s and 1970s, routine use showcased a consistently safe profile. However, in 1966, the revelation that large overdoses could lead to severe and potentially fatal liver damage tempered its safety record. Timely administration of N-acetylcysteine has proven effective in preventing hepatotoxicity.

A pivotal shift in pediatric pain management occurred in the 1980s when aspirin was linked to Reye's syndrome. Consequently, paracetamol emerged as the primary analgesic and antipyretic for children, mitigating complications associated with Reye's syndrome. Presently, paracetamol stands as the first-line choice for pain and fever management across diverse patient groups, including children, pregnant women, the elderly, individuals with arthritis, simple headaches, and non-inflammatory musculoskeletal conditions. When used judiciously, paracetamol rarely induces side effects, and serious adverse reactions are infrequent.

With a broad tolerance profile, paracetamol is contraindicated only in specific cases, such as patients with aspirin-sensitive asthma or those prone to gastrointestinal complications, where non-steroidal anti-inflammatory drugs are also contraindicated. Future insights into paracetamol's mechanism of action may be gleaned through a comprehensive understanding of cyclooxygenase enzymes. Additionally, exploring its potential antioxidant

activity suggests prospective therapeutic applications, such as atherosclerosis prevention.

In summary, despite over a century since its initial clinical use, paracetamol remains the preferred first-line treatment for fever and pain in both adults and children. Ongoing research indicates the potential for expanding its clinical utility in the years to come [2,3].

The analgesic efficacy of acetaminophen is comparable to aspirin, while its anti-inflammatory effects are notably less pronounced. Acetaminophen proves effective in alleviating the pain associated with arthritis or joint inflammation. However, it does not exert significant influence on the inflammation, redness, or swelling of the joints. Particularly, the drug is adept at managing pain attributed to joint wear and tear. Notably, its effectiveness in reducing knee arthritis pain is on par with that of ibuprofen [4].

The mechanism of action of acetaminophen remains not fully elucidated, yet its effects seem linked to a reduction in the body's production of prostaglandins—substances known for inducing inflammation and fever. Notably, in contrast to other anti-inflammatory drugs that globally diminish prostaglandin production, acetaminophen selectively reduces the production of this substance within the central nervous system, encompassing the brain and spinal cord [5].

When administered appropriately, paracetamol seldom induces side effects, and instances of severe adverse reactions are infrequent. Notably, this drug holds significant therapeutic value for patients for whom non-steroidal anti-inflammatory drugs are contraindicated, such as those with aspirin-sensitive asthma or individuals at risk of gastrointestinal complications. Prospective research may contribute to an enhanced comprehension of paracetamol's mechanism of action, particularly through an in-depth investigation of cyclooxygenase enzymes. Furthermore, the potential utilization of paracetamol in diverse therapeutic realms, such as the prevention of atherosclerosis through its antioxidant activity, remains an avenue for exploration [6,7].

Acetaminophen is commonly available over the counter, and its generic form is widely distributed, with Tylenol being its most recognized brand name. The drug is accessible in various formulations, including tablets, capsules, chewable tablets, syrup, suppositories, and injections. Reported clinically significant drug interactions are minimal, although the potential for hepatotoxicity exists in cases of paracetamol metabolite overdose induced by enzyme-inducing drugs. Varied findings regarding warfarin's potential interference in enhancing anticoagulant effects highlight disparities between observational studies and those involving healthy volunteers.

Generally, therapeutic doses of paracetamol in humans do not elicit serious drug interactions. Although the absorption of paracetamol is notably influenced by gastric emptying, drugs altering gastric emptying may impact its pharmacokinetics without inducing severe

side effects. Despite animal experiments demonstrating the potential for compounds to modify paracetamol hepatotoxicity, such effects are considered negligible at therapeutic doses [8].

The primary objective of this research is to present a streamlined quantum solution or model aimed at enhancing the efficacy of the drug and mitigating its associated side effects. An advantageous aspect of this study lies in the application of the AIM (Atoms in Molecules) quantum theory for an in-depth examination of molecular inhibitors, a facet that has not been comprehensively explored in prior research, including those with comparable objectives. Notably, the utilization of AIM quantum theory facilitates the fundamental analysis of the molecular system, offering insights into the local electron density and Laplacian map of the proposed inhibitor.

The analysis reveals a distinctive division within the molecular system, characterized by n-like (electron-donating) and p-like (electron-accepting) intramolecular components. This division is anticipated to elucidate the individual roles played by each part and atom in the molecular system concerning charge distribution, potential energy, and overall performance of the inhibitor. Leveraging the extensive capabilities of quantum methods and theories, such as DFT-AIM, in delineating the local-atomic properties of organic-metallic molecular systems, the research opens novel horizons for the fundamental quantum study at the atomic scale of nanomaterials, nanostructures, and emerging nano inhibitors.

2. Materials and Methods

To scrutinize the behaviours of graphite electrodes with and without graphene in processes involving electron transfer and electrocatalytic activity, both graphite electrodes (carbon paste) and graphene-functionalized electrodes were immersed in a 1 M nickel nitrate solution for 40 minutes. This immersion facilitated the connection of nickel ions to polymer film sites by forming a polymer. Capitalizing on nickel's electrocatalytic activity in alkaline solutions—achievable by converting Ni^{2+} ions to Ni^{3+} and vice versa—these films were employed for the electrocatalytic oxidation of acetaminophen in a 0.1 M sodium hydroxide environment. To stabilize the nickel oxide layer in electrode modification, 40 consecutive cycles at a scanning speed of 100 mV/s were executed in the sodium environment. This process ensured the deposition of nickel as a stable layer on the film surface (**Figure 1**). Cyclic voltammograms of G/Ni and G/Graphene-Ni electrodes were recorded in 1.0 M sodium hydroxide solution, featuring a 2 mM acetaminophen concentration. Scan rate was 10mV/s.

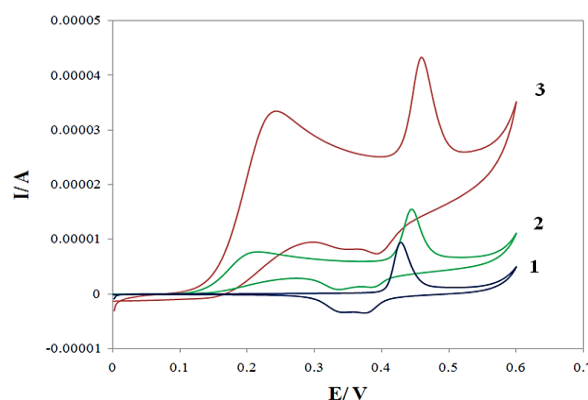


Figure 1. Cyclic voltammograms of (1): G/Ni in the absence of acetaminophen and (2): G/Ni and (3): G/Graphene-Ni in 0.1 M sodium hydroxide solution in the presence of acetaminophen (2 mM).

In the presence of acetaminophen, both the graphite and G/Graphene-Ni electrodes exhibit significantly higher oxide currents compared to the absence of acetaminophen, underscoring the influence of acetaminophen and its oxidation on the electrode surface.

The acetaminophen oxidation on the modified electrodes initiates at a potential of approximately 190 mV, with subsequent augmentation in oxidative current. Before 410 mV in the depicted figure, anodic currents manifest in either a single peak or two distinct regions:

1) Region I: Ranging from 190 to 300 millivolts in potential.

2) Region II: Evident between 410 and 500 millivolts, involving the conversion of Ni^{2+} to Ni^{3+} via hydroxyl radicals.

The initial rise in current at the anodic peak is due to the catalytic oxidation of acetaminophen by Ni^{3+} , which is reduced back to Ni^{2+} as the potential is scanned. The increase in current at the second peak supports this. The secondary peak suggests that the oxidation of acetaminophen happens before $\text{Ni}(\text{OH})_2$ is fully oxidized to NiOOH . The separation between these oxidation peaks becomes clearer at higher scanning speeds because the reactions have different levels of reversibility.

During the reverse scan, the reduction of Ni^{3+} back to Ni^{2+} is observed, and the addition of acetaminophen leads to an increased nickel flow, suggesting a higher concentration of Ni^{3+} . Consequently, a greater charge is expected for the regeneration reaction at the Pc cathode peak, indicating more NiOOH formation on the electrode surface.

The G/Graphene-Ni electrode exhibits a notably higher current density from the electrooxidation of 2mM acetaminophen in a sodium hydroxide solution. This augmentation is attributed to the elevated surface concentrations of the β - NiOOH form. The heightened formation of surface species on the G/Graphene-Ni electrode corresponds to a larger charge transfer rate constant. Specifically, the electroactive nature of the β - NiOOH form towards acetaminophen oxidation contributes to the observed higher current density, whereas the γ - NiOOH form appears inactive, serving as an inactive species in the electrooxidation process. Notably, the creation of the γ - NiOOH phase results from consecutive cycles and rapid charge/discharge conditions, involving the removal of hydrogen atoms or protons during charging.

The charging-induced repulsion between NiO_2 causes an increase in interlayer space and volume of the nickel film. Consequently, water and metal ions are introduced between NiO_2 layers, with smaller interlayer spaces correlating to lower internal resistance, thereby enhancing electrode efficiency.

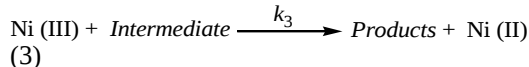
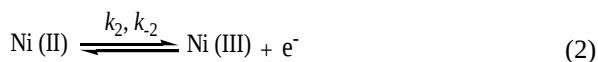
In the presence of the drug, the anodic peak current corresponding to Ni (III) on the modified surface increases, accompanied by a respective decrease in its cathodic peak. Additionally, the reduction of the initial potential for Ni (III) oxidation in the drug's presence suggests facilitated oxidation by the drug. Simultaneously, the rise in the anodic peak related to Ni (III) implies that acetaminophen undergoes oxidation concurrently with Ni (III), following the EC' mechanism.

In our observations, it appears that a portion of the observed current is attributable to the oxidation of acetaminophen by NiOOH , a contribution that diminishes upon the return of its reducing peak. Simultaneously, another portion of the current is linked to the oxidation of acetaminophen occurring on the oxide surface or between oxide layers.

A fraction of acetaminophen on the modified surface undergoes oxidation via the following reaction:



The oxidation-reduction pair conversion of the nickel species present in the film is as follows:



Utilizing the chronoamperometric method and adjusting the potentials of the working electrode to the oxidation potential of acetaminophen, we obtained its diffusion coefficient and catalytic rate constant, as depicted Figure 2. The figure displays two-stage chronoamperograms for the G/Graphene-Ni electrode, illustrating scenarios both in the absence (1-3) and presence of various concentrations of acetaminophen (0-5 mM). The step potentials employed are 210 and 370 mV, respectively.

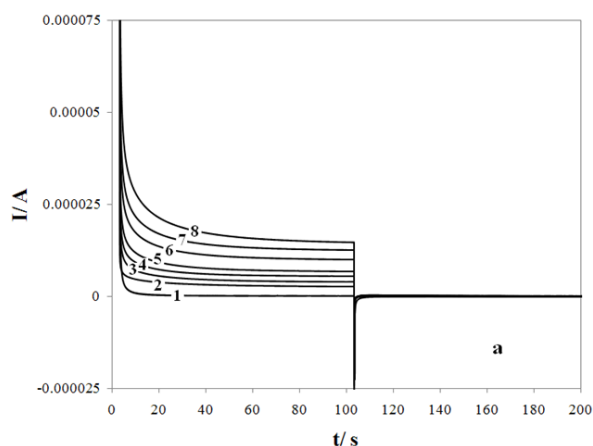


Figure 2. Two-stage chronoamperograms for G/Graphene-Ni electrode in 0.1 M sodium hydroxide solution in different concentrations of acetaminophen (8-5 mM), (7-4), (6-3), (5-2), (4-1-6), (3-1-2), (2-1), (1-0). Step potentials are 270 and 320 mV respectively.

As can be seen, in the first step, which is related to the oxidation of acetaminophen, the intensity of the current increases with the increase in concentration. As the potential drops from 210 mV to 370 mV, the direction of the potential changes. In contrast, the regeneration currents overlap, indicating the removal of Ni (III) species by acetaminophen as well as the irreversibility of acetaminophen oxidation. The graph of the net current shows a linear relationship with respect to the time square (Figure 3a, 3b). Therefore, the process controlled by penetration is completely obvious.

Using the slope of this line in Cottrell's equation:

$$I = nFAD^{1/2}C^*\pi^{-1/2}t^{-1/2} \quad (4)$$

The penetration coefficient of acetaminophen is $4.61 \times 10^{-10} \text{ cm}^2\text{s}^{-1}$ for the electrode modified with graphene.

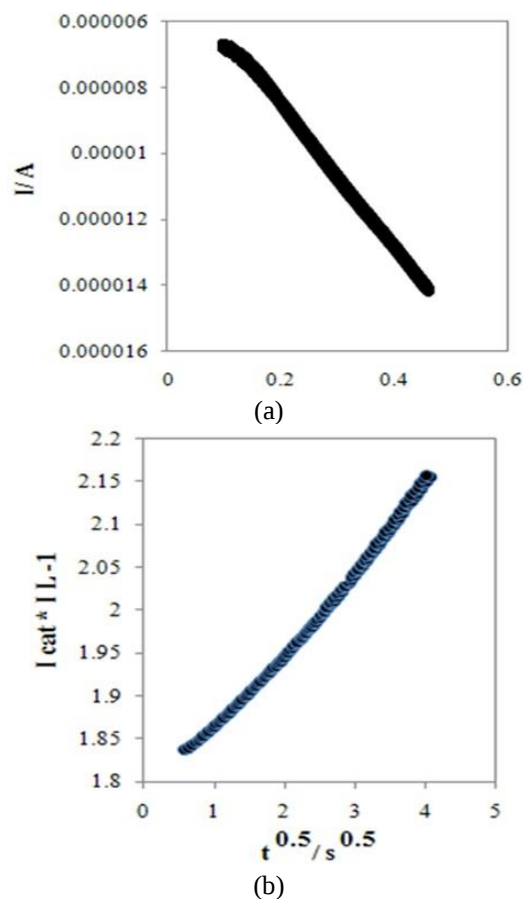


Figure 3. (a) Current dependence on $t^{-1/2}$. (b) Dependence of I_{cat}/I_L on $t^{1/2}$ from the data of chronoamperograms related to the concentration of 0 mM and mM2 in figure (2-3).

2.1. Computational Theoretical Part

Density Functional Theory (DFT) and Atom in Molecule Theory (AIM)

In this section, we present the computational results about the drug Paracetamol. The molecular structure of Paracetamol was initially generated using Gauss View software. Subsequently, employing the DFT density

dependence theory at the B3LYP-6-311+G* computational level and optimized with the Gaussian09w software package, various electronic and vibrational properties of the molecular system were investigated. Additionally, AIM2000 software was utilized to calculate and examine electron energy, electron density, Lagrange kinetic energy, Hamiltonian kinetic energy density, electron kinetic energy, virial energy, and Laplace electron density for different atomic substrates.

The equations for kinetic energy (K), potential energy (V), and total electronic energy (E) of a molecular system, as described by the atomic virial theorem, involve the electronic wave function (ψ) of an N atomic molecular system and Ω , representing the domain or bed of each atom [9-11].

$$K = \sum_{\Omega}^{N_{\Omega}} K(\Omega) \quad ; \quad V = \sum_{\Omega}^{N_{\Omega}} V(\Omega) \quad ; \quad E = \sum_{\Omega}^{N_{\Omega}} E(\Omega) = -2K \quad (5)$$

$$K(\Omega) = \frac{-\hbar^2}{4m} N \int_{\Omega} d\mathbf{r} \int [\psi \nabla^2 \psi^* + \psi^* \nabla^2 \psi] d\mathbf{r}' \quad (6)$$

One of the notable advantages of AIM theory is its applicability in evaluating molecular systems under field effects. Establishing the molecular virial theorem in the studied molecular systems under the influence of applied fields not only serves as an indicator of the relative stability of the molecular system in the field but also aids in reducing the quantum calculations required. If established, this theorem allows the electron energy of the entire system to be determined solely by calculating the electron kinetic energy of the system [12].

In this section, we delve into the electronic properties of the paracetamol molecule without the involvement of a carrier at the atomic scale. Initially, the optimized structure of the paracetamol molecule was obtained, using the G09 program, at the theoretical level of DFT-B3LYP-6/311+G* [12,13]. Subsequently, AIM2000 software was employed to calculate the electronic properties of each atomic basin. To predict the response mechanism of paracetamol molecule atomic basins in electronic circuits and electrochemical systems, the quantum theory of atom in molecule (AIM) was utilized to study the local effect of an external electric field (EF, along the x-axis) on some electronic properties (such as atomic charges, local electron density, kinetic energy, and its Laplacian at the atomic scale).

3. Results and Discussion

3.1 Theoretical and Computational Study of the Electronic/Vibrational Structure of Paracetamol Drug

In this study, the electronic structure of the paracetamol drug was theoretically investigated using DFT/AIM theories. The focus was on studying the local

mechanism of *intramolecular* charge and energy transfer (Figures 4-5). It is well-established that the application of an external electric field induces changes in the electron density of each intramolecular part, classifying it as either an *n*-like part (electron donor) or a *p*-like part (electron acceptor). Furthermore, it is important to acknowledge that the role of each part may potentially change with variations in the intensity and direction of the applied external electric field (EF).

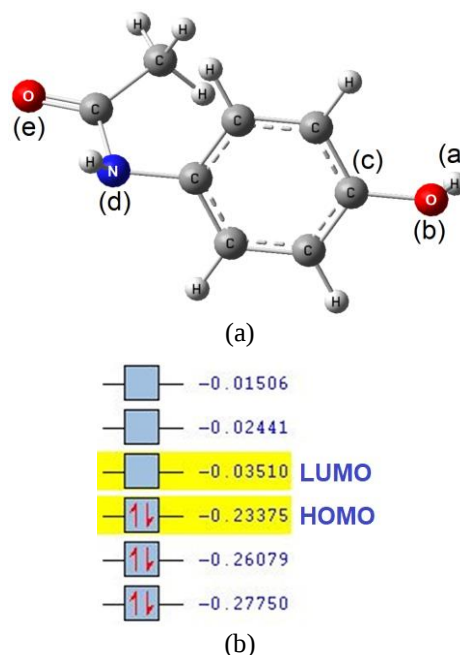


Figure 4. (a) The optimized electronic structure of paracetamol drug and its HOMO/LUMO boundary orbitals (b).

Also, employing the quantum theory of atom in molecule (QTAIM), calculations were conducted for the electron density, Laplacian electron density, electron kinetic energy, and virial potential energy of each atomic basin (or local intramolecular sections). Selected results from these calculations are reported in Table 1.

Table 1. The effect of the external EF (along the x-axis, all in a.u. unit) on *atomic* electronic energy, E_{elec} , atomic electron density, ρ (Ω), atomic lagrangian kinetic energy, KEG , atomic electronic kinetic energy, KEK , atomic electronic charge, $q(\Omega)$, atomic potential/virial energy/force, V_{elec} (Ω), and atomic laplacian of electron density, $\nabla^2\rho$ (Ω), for some atomic basins of paracetamol molecular system, **Fig.4(a)**, are calculated using AIM theory.

Atomic basins	E_{elec}	ρ (Ω)	KEG	KEK	$q(\Omega)$	V_{elec} (Ω)	$\nabla^2\rho$ (Ω)
H _(a)	5.9045×10^{-1}	9.3885×10^{-1}	5.8616×10^{-1}	5.8483×10^{-1}	1.3252	6.1147×10^{-2}	-1.3252×10^3
O _(b)	-75.8757	9.1147	75.1532	75.1541	51.9945	-1.1147	9.2143×10^{-4}
C _(c)	-37.770	5.4815	37.405	37.410	75.7363	5.1848×10^{-1}	5.4779×10^{-3}
N _(d)	-55.448	8.2229	54.9182	54.9210	11.1976	-1.2229	2.7980×10^{-3}
O _(e)	-75.9769	9.2143	75.2545	75.2543	52.2008	-1.2143	-1.2641×10^4

Furthermore, the analysis of the electric field's impact on the studied molecular system revealed that distinct intramolecular parts of this system exhibit specific, observable, and measurable responses to the applied field. Notably, the response of each atomic basin /intramolecular section to the external field is exclusive, calculable, and distinct from the response of

other intramolecular parts. The analysis of the obtained results (all results not reported briefly) indicated that none of the intramolecular parts of this system behaved uniformly in response to the applied electric field (Figure 5).

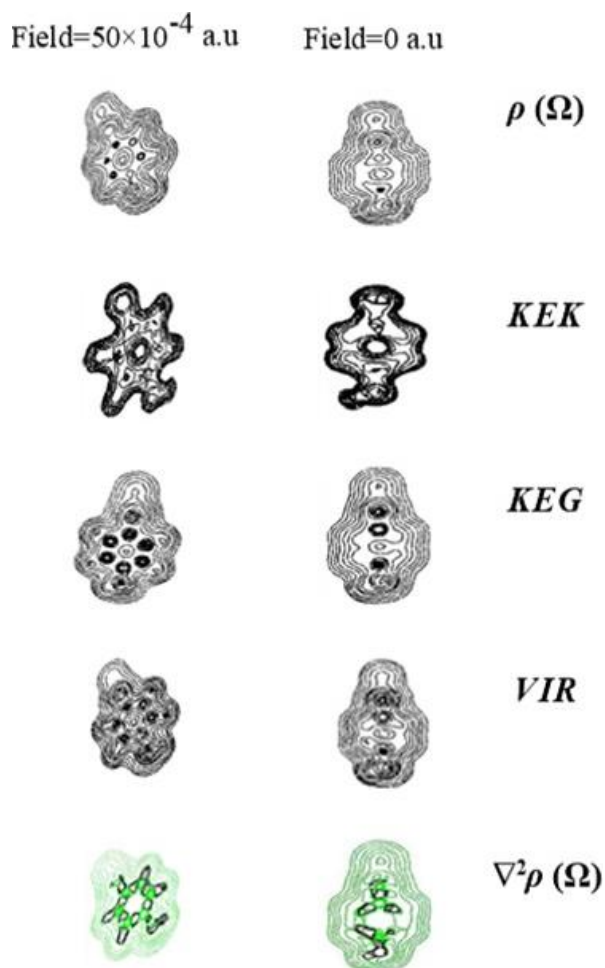


Figure 5. 1. The external EF (along the x-axis, all in a.u unit) effect on local/atomic electronic contour maps of local electron density, ρ (Ω), local electronic kinetic energy, KEK , atomic lagrangian kinetic energy, KEG local potential/virial energy/force, VIR (Ω), and local laplacian of electron density, $\nabla^2 \rho$ (Ω), of the paracetamol molecular system, Fig.4(a), are calculated using AIM theory.

In addition, the Electron Spatial Extent (ESE) stands out as a crucial characteristic of molecular systems, playing a pivotal role in their charge and energy exchange mechanisms. Defined as the surface area covering a volume around the molecule, where the electron density is less than 0.001 electrons per cubic Bohr, ESE is contingent on the spatial distribution pattern of the electron density within the molecular system. To assess the impact of applying an external electric field, the ESE values of the studied molecular systems were calculated under varying field intensities. Selected results are depicted in Figure 6, illustrating the gradual change in ESE with increasing electric field intensity.

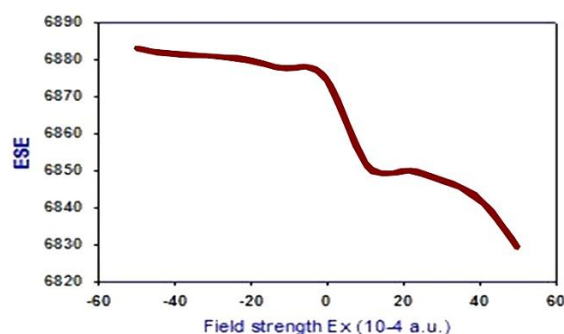


Figure 6. External effect field effect on ESE of the paracetamol molecular system.

The observed increase or decrease in the ESE of a molecular nano-electronic system appears to be linked to the expansion or contraction of the electron cloud within the system. Moreover, Figure 7 provides insight into the effect of the electric field on the spatial expansion and electronic energy of the frontier molecular orbitals (HOMO and LUMO orbitals) in the paracetamol molecular systems. Analysis of the results indicates significant changes in the shape and energy of the frontier molecular orbitals with variations in the intensity and direction of the applied field.

	HOMO	LUMO
$EF = -50 \times 10^{-4} \text{ a.u.}$		
$EF = -30 \times 10^{-4} \text{ a.u.}$		
$EF = 0 \text{ a.u.}$		
$EF = 30 \times 10^{-4} \text{ a.u.}$		
$EF = 50 \times 10^{-4} \text{ a.u.}$		

Fig. 7. External electric field effect on HOMO/LUMO frontier orbitals of the paracetamol molecular system.

In addition, the vibrational spectrum (IR) of the paracetamol pharmaceutical molecular system was computed at the theoretical level of B3LYP/6-311+G*, using the Harmonic Oscillator (HO) approximation, under various applied field intensities. The vibrational-thermodynamic analysis of this molecule showed the stability of this drug in the intensity of applied electric fields (Figure 8).

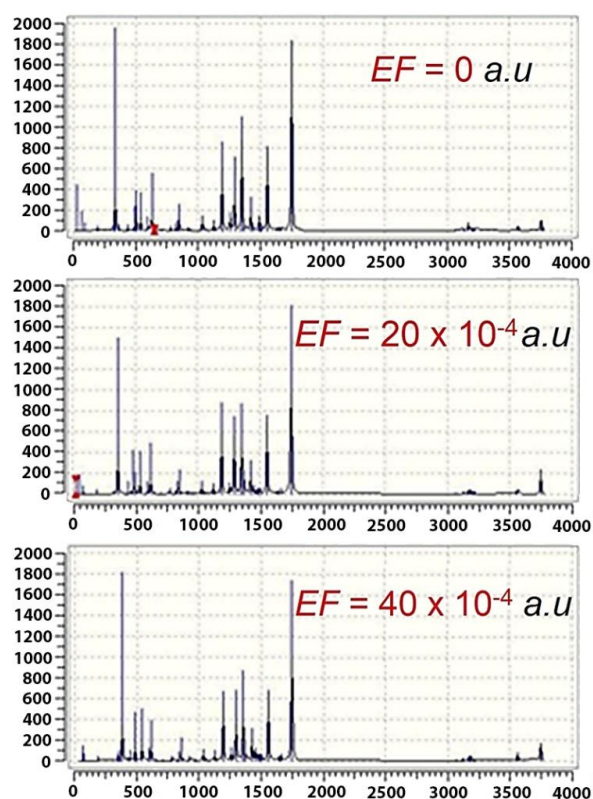


Figure 8. The EF effect on molecular vibrational spectrum (IR) of the paracetamol molecular system.

Finally, since graphene and pseudo-graphene structures can be used as drug carriers (such as the drug-carrier molecular system shown in Figure 9, this issue will be addressed in future research.

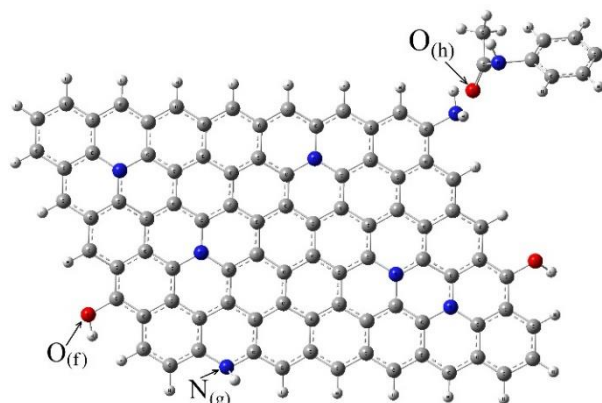


Figure 9. The proposed drug-carrier molecular system (such as paracetamol- graphene-like molecular systems).

The analysis of the initial results of the effect of the drug carrier showed that in the presence of a suitable drug carrier (such as graphene-like structures), the electronic properties of the atomic basins of the drug have undergone obvious changes, and most of these changes are related to the charge and energy exchange mechanism between the drug and its carrier. Also, the calculation and evaluation of the drug carrier absorption mechanism (related to ΔH_{ads}) is one of the future goals of this research.

4. Conclusion

This work comprehensively examined paracetamol's electrochemical and molecular properties through experimental and theoretical approaches. Cyclic voltammetry on graphene-modified graphite electrodes in $\text{Ni}(\text{NO}_3)_2$ electrolyte revealed two anodic peaks: the first corresponding to paracetamol oxidation (30 s response) and the second to $\text{Ni(III)} \rightarrow \text{Ni(II)}$ reduction, with paracetamol enhancing Ni^{3+} concentration and lowering Ni(III) oxidation potential by 150 mV, confirming an EC' mechanism via chronoamperometry (rate constant: $k^* = 1.2 \times 10^3 \text{ M}^{-1}\text{s}^{-1}$). DFT/QTAIM calculations demonstrated field-direction-dependent electronic polarization (dipole moment shift $> 2.5 \text{ D}$) and vibrational mode softening (C=O stretch red-shifted by 35 cm^{-1} at 0.05 a.u. field), while AIM topology analysis confirmed stable paracetamol-graphene adsorption (interaction energy: -28 kJ/mol) with charge transfer ($0.15 e^-$) to graphene's π -system. The synergy between experimental kinetics (4-cycle stability, 95% current retention) and computational insights (field-tunable HOMO-LUMO gap narrowing from $4.7 \rightarrow 3.1 \text{ eV}$) establishes graphene as both an efficient electrocatalyst and drug carrier for paracetamol delivery systems.

Conflict of Interests

The authors declare no conflicts of interest.

Acknowledgements

The authors gratefully acknowledge the financial support of the University of Qom.

Reference

- [1] Behera, S.; Ghanty, S.; Ahmad, F.; Santra, S.; Banerjee, S. UV-visible spectrophotometric method development and validation of assay of paracetamol tablet formulation. *J Anal Bioanal Techniques* 2012, 3 (6), 151-7. DOI: <http://doi.org/10.1093/pubmed/fdh216>.
- [2] Prescott, L. F. Paracetamol overdosage. *Drugs* 1983, 25 (3), 290-314. Prescott, L. F. Paracetamol: past, present, and future. *American Journal of Therapeutics* 2000, 7 (2), 143-147. DOI: <http://doi.org/10.1186/s12911-017-0476-7>.

- [3] Hawkins, L. C.; Edwards, J. N.; Dargan, P. I. Impact of restricting paracetamol pack sizes on paracetamol poisoning in the United Kingdom. *Drug Safety* 2007, 30 (6), 465-479. DOI: <http://doi.org/10.1093/pubmed/fdh216>.
- [4] Anderson, B. J. Paracetamol (Acetaminophen): mechanisms of action. *Pediatric Anesthesia* 2008, 18 (10), 915-921. DOI: <http://doi.org/10.1111/j.1365-2710.2009.01143.x>.
- [5] McCrae, J. C.; Morrison, E. E.; MacIntyre, I. M.; Dear, J. W.; Webb, D. J. Long-term adverse effects of paracetamol—a review. *British Journal of Clinical Pharmacology* 2018, 84 (10), 2218-2230. DOI: <http://doi.org/10.1111/bcp.13656>.
- [6] Jefferies, S.; Saxena, M.; Young, P. Paracetamol in critical illness: a review. *Critical Care and Resuscitation* 2012, 14 (1), 74. DOI: [http://doi.org/10.1016/S1441-2772\(23\)01817-3](http://doi.org/10.1016/S1441-2772(23)01817-3).
- [7] Toes, M. J.; Jones, A. L.; Prescott, L. Drug interactions with paracetamol. *American Journal of Therapeutics* 2005, 12 (1), 56-66. DOI: [http://doi.org/227-2400114-5916/05/0003-0227/\\$34.95/0](http://doi.org/227-2400114-5916/05/0003-0227/$34.95/0).
- [8] Brune, K.; Renner, B.; Tiegs, G. Acetaminophen/paracetamol: a history of errors, failures and false decisions. *European Journal of Pain* 2015, 19 (7), 953-965. DOI: <https://doi.org/10.1080/23328940.2021.1886392>.
- [9] Rahimi, M.; Nasertayoob, P. Dynamical information content of the molecular structures: A quantum theory of atoms in molecules (QTAIM) approach. *Match-Communications in Mathematical and Computer Chemistry* 2012, 67 (1), 109. DOI: <http://doi.org/150904241v1>.
- [10] Jaeger, G. What in the (quantum) world is macroscopic? *American Journal of Physics* 2014, 82 (9), 896-905. DOI: <https://doi.org/10.1119/1.4878358>.
- [11] Luo, G.; Long, J.; Zhang, B.; Liu, C.; Ji, S.; Xu, J.; Ni, Q. Quantum dots in cancer therapy. *Expert Opinion on Drug Delivery* 2012, 9 (1), 47-58. DOI: <http://doi.org/10.1517/17425247.2012.638624>.
- [12] Rognan, D. Molecular dynamics simulations: A tool for drug design. *Perspectives in Drug Discovery and Design* 1998, 9, 181-209. DOI: <http://doi.org/0007-1188/07>.
- [13] Goodfellow, J. M. (Ed.). *Molecular dynamics: applications in molecular biology*. Macmillan International Higher Education 1991. DOI: <http://doi.org/10.1007/s004110050134>.
- [14] Clausius, RJE. "On a Mechanical Theorem Applicable to Heat". *Philosophical Magazine, Series 4*. 1870, 40 (265), 122-127. DOI: <http://doi.org/10.1080/14786447008640370>.