RESEARCH PAPER

Computational Verification of Certain Polymers for Anticancer Drug Delivery Application Using DFT Module of Gaussian 16 Software

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ABSTRACT

Cancer continues to remain a major global health issue due to rising incidence and mortality rates. Traditional treatments like chemotherapy and radiotherapy often have limitations, such as systemic toxicity, low selectivity, and drug resistance. Polymer-based drug delivery systems are emerging as helpful strategies to improve treatment effectiveness and reduce side effects. This study obtains the electronic structure an calculates stability and reactivity of a fluorescent amphiphilic homopolymer, the anticancer drug doxorubicin (Doxil), and their polymer-drug conjugate using Density Functional Theory (DFT), and to evaluate their potential for targeted drug delivery. DFT calculations were conducted in Gaussian 16 software. B3LYP hybrid functional along with 6-311+G (d,p) basis set was employed in this modeling work. Molecular structures were drawn with ChemDraw software, and visualizaed in GaussView software. Key global reactivity descriptors, are mainly HOMO energy and LUMO energy, and in turn band gap, and other indicators of chemical reactivity. This evaluation helps understand molecular stability and charge-transfer behavior. The results showed that the polymer-drug conjugate exhibited a significantly reduced band gap of 1.47 eV compared with the isolated polymer (5.18 eV) and the free drug (2.1 eV). This reduction suggests stronger electronic coupling and enhanced intermolecular charge-transfer interactions after conjugation. Furthermore, the conjugate displayed increased chemical softness and moderate electrophilicity, indicating better electronic adaptability that may support efficient drug loading and controlled release. These findings emphasize that polymer-drug conjugation changes electronic properties and improves interaction capability. This provides valuable theoretical support for the design of advanced polymer-based nanocarriers for anticancer drug delivery.

Keywords: *Polymer, Doxorubicin, DFT, FMO, Drug Delivery, Chemical Reactivity, Charge Transfer*

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1. INTRODUCTION

Cancer remains a major public health challenge characterized by uncontrolled cell growth, tissue invasion, and metastasis, which are the leading causes of cancer-related mortality. In year 2022 alone, around 20 millions cancer cases, and 9.7 million cancer casualties reported globally, and this burden has being projected to reach nearly 35 million cases by 2050. Despite significant advances in anticancer therapies, conventional treatments such as surgery, chemotherapy, and radiotherapy continue to face major limitations, including systemic toxicity, poor tumor specificity, therapy resistance, and recurrent treatment failure[1]. Furthermore, anticancer drug delivery remains problematic because many chemotherapeutics exhibit low bioavailability, poor stability, non-specific distribution, and dose-related toxicity, which reduce therapeutic effectiveness and increase adverse effects. Polymeric drug-delivery systems, although promising, also present challenges such as limited drug-loading capacity, stability concerns, potential side effects, and difficulties in clinical translation. These persistent obstacles highlight the need for more efficient, targeted, and safer drug-delivery strategies to improve therapeutic outcomes and reduce cancer-associated mortality[2].

Developing and advancing materials research for improved drug delivery systems grow in rapid pace, and this uses fast growing field such as nanoscience, nanotechnology, biochemistry, biomedicine, etc, providing more thought provoking and precise innovation strategies, at the best therapeutic delivery, and an enhanced clinical performance. Traditionally used drug delivery systems have many inherent weaknesses, such as very low bioavailability, low efficiency in target specificity of action, and uncontrolled and improper drug release rates, that in turn reduce the effectiveness of therapeutics, and creates more side effects[3-6]. The materials finding

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application in drug delivery systems have a unique molecular, and physical structural architectures, with large surface area – to - volume ratio, that can usually be used to accommodate a very large amount of and a varied variety of drug molecules, via non-covalent adsorption, and electrostatic forces of attraction, or by chemical bonding. In drug carrier design and drug delivery systems, the high chemical stability of polymers or other carrier molecules ensures in maintaining the integrity of the carrier molecules under human body physiological conditions (for example, in body pH and carrier stability in other conditions of body fluids). Conjugate formation creates the adjustability in electronic structure, and surface properties of carrier molecules. It allows its best modulation of interaction between drug and substrate interactions, and controlled rate of drug's release[4,7,8].

Polymer–drug conjugates incorporating the anticancer therapeutic drug molecule and a theranostic imaging agents represent a powerful class of anticancer drugs. This combo enables the simultaneous diagnosis and treatment combined in a single platform. Diagnostic imaging methods are in use in providing the details of the target status, kinetics of drug action, and progress in disease combat. It also allows us to obtain assessing treatment effectiveness in real-time. It is an integral method of facilitating a precise activation of therapeutic action, by monitoring drug distribution in human body and its localization. Polymer based drug delivery systems are more versatile and highly tunable, making further simplified drug development, and the ease of its optimization in these anticancer drug platforms[4,8]. Recent advances in drug delivery systems research was made more in polymer-to-drug bonded conjugates, especially for target specific drug delivery, in enhancing the target specific action, and effectiveness of cancer treatment procedures, with minimal adverse side effects on neighbouring healthy cells. The research in the polymer-drug conjugate is advancing in rapid pace, more on creating the external or body pH based stimuli - responsive for delivery actions. These "polymer – drug" conjugate systems were so made in such as way that they react to specific body fluid conditions, or to an external stimuli for slow drug release, precisely when drug is required. Cancer involves body areas with acidic pH values (the fluid is in acidic pH in and around cancer cells). Target specific deployment minimizes the exposure of other cells to drug effect, and in turn, side effects to other cells, whilst maximizing therapeutic impact on cancerous cells[5,6,9,10].

Computational theoretical models are many to arrive at molecular electronic structures, Frontier's molecular orbitals (FMO's) and their energies. These models are of two major types. First type: quantum mechanics-based models, lying mainly on the laws of quantum mechanics and Schrodinger's wave equation. Second one: molecular mechanics (or molecular dynamics) based models, lying on the simple but chemically reasonable picture of the molecular structure and reaction conditions[8,11-13]. Quantum mechanics is based mainly on 2 solution schemes, viz, Hatree - Fuck method (self-consistent field theory), and Moller - Plesset method (perturbation theory). However, The important and best model to deal chemical reaction is Kohn-Sham Density Functional Theory (DFT). When compared to Hatree - Fock and Moller - Plesset methods, Kohn-Sham method (DFT) is very simple and accurate quantum chemical treatment to obtain molecular electronic structure and chemical reactivity. DFT applies the electron density (ρ) of molecules and molecular systems, instead of the many-electron complicated large wave function, ie, $\Psi(\mathbf{x}, t)$ that is used in Hatree - Fock and Moller - Plesset methods[14]. DFT uses the probability distribution of electrons described by 3 Cartesian space coordinates (x, y, z), whereas the wave function (of Hatree – Fock and Moller – Plesset methods) depends on 3N spatial coordinates (N – number of electrons in the molecular systems or reaction systems)[15]. DFT is based on electronic structure to get FMO's energies and it solves the Fermionic (or Fermi gas) systems that underlie most part of chemistry and reactions, and is useful for biology and physics too. Aligning molecular dynamics (MD), it provides potential energy surface (PES). DFT solves many problems in biochemistry too. The results are sufficiently accuracy to obtain meaningful insight on electronics structure and chemical reactivity of molecules[16,17].

DFT is a powerful method to obtain the suitability of any newly designed fluorescent amphiphilic homopolymer for drug delivery application. DFT is used to get properties of polymer, doxorubicin (doxil) anticancer drug and the polymer-drug conjugate prior to experimental studies[18]. In this work, using DFT, energy band gap has precisely obtained. Also from HOMO and LUMO energy values, electronic structure is obtained, and in turn, other chemical descriptors are obtained at the atomic level. This offers us valuable insights for rationally designing polymer-based drug carrier for drug delivery systems[19].

2. MATERIALS AND METHODS

Electronic structural optimization studies performed in DFT module of Gaussian 16 software to analyze the molecular-level interactions of the fluorescent amphiphilic homopolymer, doxorubicin (doxil) anticancer drug and polymer-doxil drug conjugate. Structures of the fluorescent amphiphilic homopolymer, doxorubicin (doxil) anticancer drug and polymer-doxil drug conjugate (complex) were designed using ChemDraw 22 software. Using the Gaussian 16 software package, the DFT calculations have been performed. The FMOs visualization performed by GaussView 06 software. To get structure of FMOs and to obtain its energies, the B3LYP hybrid functional employed. This functional is giving the precise description of molecular structures and is helping to obtain the FMO energies. So, B3LYP selected as the exchange - correlation functional in our modeling works. In B3LYP hybrid functional, B3 stands for Becke's 3 parameter exchange, whilst LYP stands for Lee-Yang-Parr correlation (LYP). This hybrid functional results in a well-balanced approach to account both short-range and long-range correlation effects. Additionally, the basis function set used in our calculation is 6-311 + G (d, p) that represent well the arrangement of carbon, hydrogen, oxygen, nitrogen, and sulfur atoms either in the polymer, or in doxil, and and also in polymer - doxil conjugate. The 6-311+G(d,p) basis set accounts well the polarized double-zeta basis set containing polarization functions for all atoms (C, H, O, N, S), and to carryout electronic property calculations. This set achieves a satisfactory balance between computing efficiency and accuracy in representing the electrical structure of so selected polymer and drug by us.

In the DFT single-point calculations, the comprehensive evaluations have performed to obtain both the global molecular characteristics, and the local molecular characteristics. From HOMO energy and LUMO energy, many parameters influencing reactivity of molecules have arrived. The numerical values of parameters are : E_{HOMO}, E_{LUMO}, and $\Delta E = E\text{gap}$. From these three values (HOMO energy, LUMO energy and Egap), chemical reactivity parameters such as ionization energy or potential, I; electron affinity, EA; electronegativity, χ; molecular hardness, η; molecular softness, S; electrophilicity, ω; and chemical potential, μ are calculated. These are commonly used identities or Eigen values, representing various energy-related properties, and in turn chemical reactivity that correlates to drug encapsulation in polymer and time dependent slow drug release from polymer.

The symbol for band gap is E_{gap}. It is energy difference existing between the two states, E_{LUMO} and $E_{HOMO.}$ It represents the minimum energy required to excitation transfer an electron from the valence band of chemical bond (electron in covelent bond) to the conduction band (electron in interstice or conjugate bonded orbital). A smaller gap, lower Egap indicates the molecules is higher in chemical reactivity, lower in the stability (inertness), and higher in the polarizability. A larger gap, higher Egap indicates that the molecule is a hard molecule with lower chemical reactivity and greater inertness or stability. This energy gap, Egap also defines the optoelectronic properties of polymers, or doxil drug. Egap value (unit usually is eV) determines the types of materials, viz, a material is a conductor, or a semiconductor, or an insulator when electrically connected in circuit. The ionization energy (IE or *I*) is directly obtainable to the energy of the HOMO via an approximation of Koopmans' theorem and in this context. The energy of the HOMO is typically negative in DFT calculations, making the Ionization Energy a positive value. The E_{HOMO} is mostly always negative for stable molecules. Its magnitude of negative of the Eigen value (i.e., $-E_{HOMO}$).

On the basis of Koopman's theorem, Electron Affinity (EA) is nothing but negative value of lowest unoccupied molecular orbital (E_{LUMO}), ie, $EA = - E_{LUMO}$. Specifically, the electron affinity, by definition, is the negative of the LUMO energy: ($-E_{LUMO}$). This correlation suggests that a lower (more negative) E_{LUMO} value correlates with a higher electron affinity. More the EA value is indicative of greater tendency for the molecule to accept electrons. Global or chemical softness (*S*) is a descriptor of a molecule's overall reactivity and polarizability, representing how easily its electron cloud can be deformed or manipulated during a chemical reaction. Mathematically, the parameter S is the reciprocal of global chemical hardness**.** Soft Molecules (High Softness): Characterized by a small HOMO-LUMO energy gap ($\Delta E = E_{LUMO}-E_{HOMO} = Eg$), high polarizability, and high chemical reactivity. Hard Molecules (Low Softness): Characterized by a large HOMO-LUMO energy gap, low polarizability, and higher kinetic stability. More the softness the molecule are very reactive, such as a strong Lewis base, or a soft nucleophile.

Chemical potential (μ) is the average energy value of the two FMOs. $M=(E_{HOMO}+E_{LUMO})/2$. It is a measure of molecule's escaping tendency for electrons, and in turn it indicates molecules chemical reactivity directly. Based on Koopman's theorem, it represents the midpoint of the frontier molecular orbitals gap. A higher (less negative) chemical potential implies a greater tendency to donate electrons. A lower (more negative) value indicates a tendency to accept electrons. Typically, E_{HOMO} and E_{LUMO} are in electron volts (eV), making a measure of the system's electronic stability and chemical reactivity of a molecule. Electronegativity is the ability of an atom or a molecule to attract and abstract electrons, derived from Koopmans' theorem that relates these orbital energies to the Ionization Potential and Electron Affinity. It is calculated as $\chi = - \mu$. Higher (more positive or less negative) value suggests a higher tendency to pull electrons towards it. Electrophilicity index (ω) is a quantitative, and a global reactivity descriptor. It measures an atom's or a molecule's property or its capacity to accept electron density. It defines the stabilization energy a system gains when it receives an electron. This index (ω) allows for the classification of molecules on a numerical scale.

The combined interpretation of FMO parameters and global reactivity descriptors provides a comprehensive electronic profile of DFT-optimized systems. HOMO energies and LUMO energies offer direct insight into excitation, and redox behavior. But the derived descriptors, such as chemical hardness and softness, electronegativity and chemical potential (partial molar Gibb's free energy), and electrophilicity index enable quantitative evaluation of molecular stability, charge transfer potential, interaction strength, and reactivity trends, together, these parameters bridge quantum chemical calculations with physicochemical behavior, facilitating rational design and optimization of polymer-drug conjugates for advanced biomedical applications.

GaussView 6.0 software serves 3D visualization of molecular structure, and as structural analysis platform in various angles and directions, enabling the structural refinement, and in the calculation of key molecular properties, such as the vibrational frequencies (IR spectra), and energy states (UV-Visible spectra). From spectral analyses, more information on molecular structure and its properties (for example, chemical reactivity) are obtainable.

3. RESULTS AND DISCUSSION

3.1. Electronic structure and band gap

Figure 1 shows molecular systems (polymer-drug duo) used for verification of polymer for anticancer drug delivery systems. The polymer is a newly synthesized molecule in our laboratory[4]. The drug is a purchased molecule from market. Figure 2 shows the electronic structure of polymer, drug, and polymer – drug conjugate used in our study. This figure was created by DFT module of Gaussian 16 software. These structures clearly show the HOMO and LUMO of polymer molecules, drug molecule, and polymer – drug conjugate. The Gaussian 16 software provides us with data to derive many other data as shown in Table 1. This table shows 8 descriptors calculated from energies of FMO's, HOMO and LUMO.

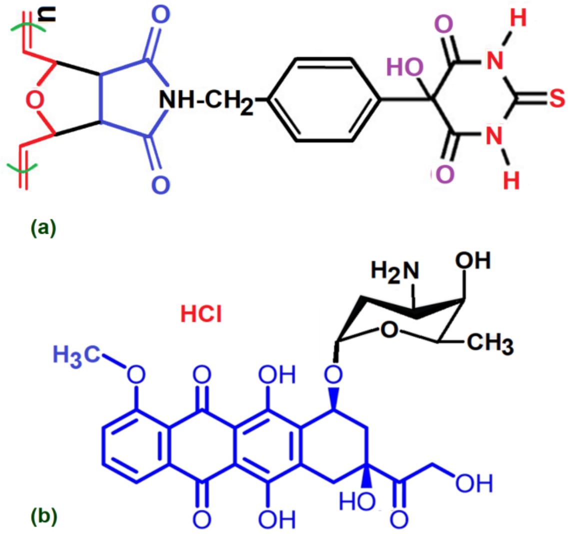

Fig.1 Molecular structures: (a) Polymer, (b) Doxyl. This polymer and drug forms bond by electrostatic interaction. So, Polymer-Drug conjugate forms third molecules for our analysis.

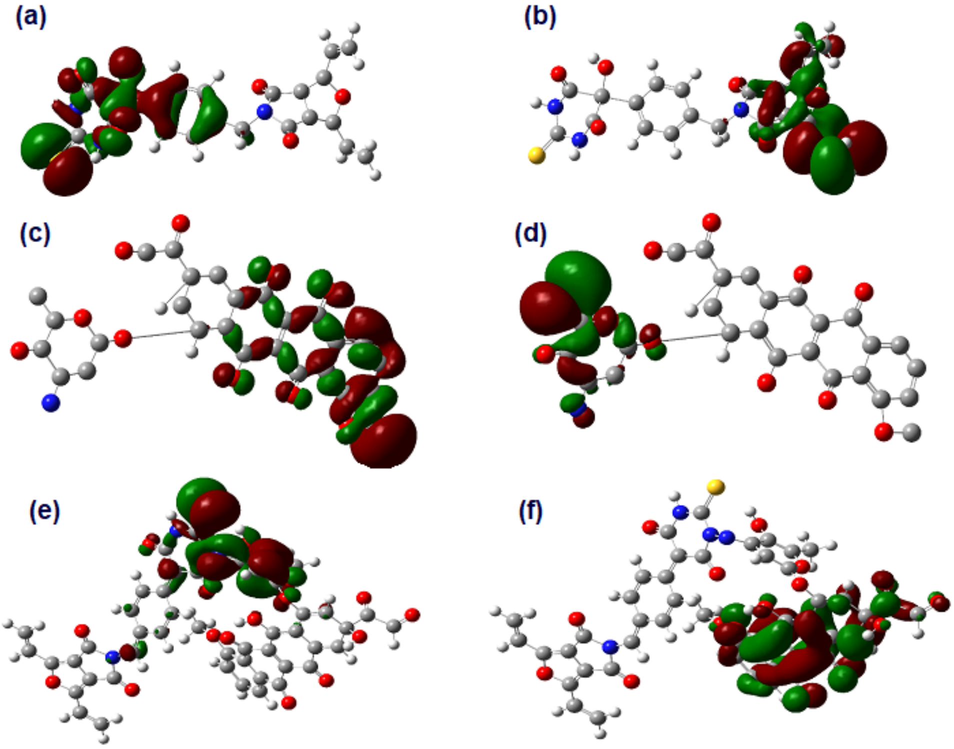

Fig.2 (a) HOMO of Polymer, (b) LUMO of Polymer, (c) HOMO of Doxil, (d) LUMO of Doxil, (e) HOMO of Polymer-Doxil Conjugate, and (f) LUMO of Polymer-Doxil Conjugate

Table 1. Summary of Density Functional Theory (DFT)-derived global reactivity descriptors calculated for the isolated polymer, free drug, and their polymer-drug conjugate, highlighting electronic structure modulation and reactivity enhancement upon conjugation.

S.No.	Chemical Descriptors	Polymer	Drug	Polymer – Drug Conjugate
1	**Band Gap, ΔE (eV)**	5.18	2.1	1.47
2	**Ionization Potential, I (eV)**	6.67	7.41	5.85
3	**Electron Affinity, A (eV)**	1.49	5.31	4.38
4	**Chemical Hardness, η (eV)**	2.59	1.05	0.74
5	**Chemical Softness, S (1/eV)**	0.19	0.48	0.68
6	**Electronegativity, χ (eV)**	4.08	6.36	5.12
7	**Chemical Potential, μ (eV)**	-4.08	-6.36	−5.12
8	**Electrophilicity, ω (eV)**	3.21	19.26	17.83

The electronic structure of pharmaceutical delivery systems critically determines their chemical reactivity, charge-transfer capacity, optical behavior, and intermolecular interactions that govern drug loading, release kinetics, and bioavailability. The calculated HOMO-LUMO energy gaps (ΔE) provide fundamental details of electronic structures of molecules, stability, potential, and reactivity of the polymer, drug, and polymer-drug conjugate systems. The band gap values reported in Table 1 demonstrate a systematic narrowing from the isolated polymer (5.18 eV) to the free drug (2.1 eV) and most prominently to the polymer-drug complex (1.47 eV). This is reflecting the progressive modification of frontier orbital energies, enhanced electronic delocalization, and the emergence of intermolecular charge-transfer interactions upon complex formation. Wide band gap of 5.18 eV indicatives the high kinetic stability and strong resistance to charge transfer. The large band gap observed for the polymer is characteristic of saturated or weakly conjugated pharmaceutical carriers such as PEG, PCL, or cyclodextrin derivatives, which lack extended π-electron delocalization and exhibit localized frontier orbitals. Such electronic architecture confers high chemical hardness, low intrinsic reactivity, and resistance to oxidation or reduction, attributes desirable for excipients that must remain stable under physiological conditions. Literature reports of similar systems consistently show HOMO-LUMO gaps in the 4.3-5.0 eV range, attributed to limited orbital overlap and predominantly van der Waals-driven host-guest interactions. Thus, the polymer's wide gap reflects structural stability and electronic inertness, ensuring minimal unintended reactivity during storage and systemic circulation. Large gap also indicates insulating or semiconducting behavior meaning that the system is not conductive at room temperature at which it is typical for organic pharmaceutical molecules and polymer carriers[9,10,12,13,16]. Overall, significance for drug delivery includes**:** high stability during storage and circulation, low risk of unwanted redox reactions with biological molecules, predictable behavior in physiological environments, and minimal photochemical degradation.

In contrast, the drug's intermediate band gap of 2.1 eV corresponding to an excitation wavelength in the visible region (≈590 nm), consistent with π-conjugated aromatic frameworks capable of supporting lower-energy electronic transitions aligns with the electronic characteristics of aromatic, heteroatom-containing pharmaceutical molecules possessing partial π-conjugation[9]. Such systems display moderate electron delocalization, elevated HOMO energies, and stabilized LUMO levels, resulting in enhanced redox flexibility and greater interaction capability with biological targets and carrier matrices. Band gaps within the 1.7-3.3 eV range are commonly reported for bioactive small molecules and correlate with absorption in the UV-visible region, supporting optical detection and redox-mediated biological activity. Computational studies of tamoxifen, β-blockers, and favipiravir adsorbed onto polymeric or graphene-based carriers demonstrate comparable intermediate gaps that decrease upon complex interactions such as π–π stack formation, hydrogen bond formation and electrostatic interactions. The moderate band gap of the drug suggests a greater intrinsic reactivity and redox flexibility, properties that may contribute to its biological activity through interactions involving electron transfer, hydrogen bonding, or π–π stacking with biomolecular targets[5,6,8,14].

The most significant finding is the pronounced reduction of the band gap to 1.47 eV in the polymer-drug complex, representing a 71.6% decrease relative to the polymer and approximately 30% relative to the free drug establishes an electronic gradient favorable for donor-acceptor interactions upon conjugation. This substantial narrowing indicates strong electronic coupling and formation of new delocalized frontier orbitals spanning both components. Intermolecular interactions particularly π–π stacking (≈3.0–3.5 Å), hydrogen bonding (≈1.8–2.2 Å), and electrostatic attractions facilitate orbital hybridization and ground-state charge transfer, stabilizing the LUMO and/or destabilizing the HOMO, thereby reducing ΔE. Similar gap reductions have been documented in graphene oxide-drug systems, chitosan-drug complexes, and surfactant-based nanocarriers, where naturally bonded orbitals, and reduced electron density gradient analyses confirm charge redistribution across host - guest interfaces[19]. Most notably, the polymer-drug conjugate displays a dramatically reduced band gap of 1.47 eV, corresponding to near-infrared excitation (≈843 nm), which is lower than that of either isolated component. This pronounced reduction provides strong theoretical evidence of electronic coupling and the emergence of new frontier molecular orbitals delocalized across both fragments. The trend $\Delta E_{\mathbf{polymer}}$ (5.18 eV) > $\Delta E_{\mathbf{drug}}$ (2.10 eV) > $\Delta E_{\mathbf{conjugate}}$ (1.47 eV) clearly demonstrates the formation of low-energy electronic states that are absent in the individual systems. Such a decrease in band gap is typically associated with donor-acceptor orbital interactions, extended conjugation, and charge-transfer (CT) state formation, whereby electron density is redistributed between polymer and drug moieties to produce stabilized, lower-energy excitations[11]. Overall, the systematic and substantial reduction in band gap upon conjugation provides compelling computational evidence of strong electronic communication between the polymer and drug, the generation of new delocalized frontier orbitals, and the emergence of charge-transfer character in the hybrid system. The band gap analysis therefore serves as a critical bridge between quantum chemical calculations and functional behavior, linking electronic structure modifications to predicted optical properties, interaction strength, and potential biological performance in polymer-based drug delivery platforms.

3.2. Ionisation Potential and Electron Affinity

Ionization potential (I) is - E_{HOMO} (negative value of energy of HOMO) according to Koopman's assumptions in DFT. It is an important descriptor for evaluating the electronic stability and reactivity of molecular systems providing an important insight into the electron-donating ability and redox behavior of the studied systems. In general, lower ionization potential indicates that electrons can be removed more easily from a molecule, implying stronger electron-donating ability and greater chemical reactivity used in drug delivery. In the present study, the calculated ionization potentials follow the trend: Doxil (7.41 eV) > polymer (6.67 eV) > polymer-Doxil conjugate (5.84 eV). The relatively high IP value of Doxil indicates a strong resistance to electron removal, suggesting that the drug molecule possesses considerable electronic stability. This behavior is attributed to the highly conjugated aromatic anthracycline core of doxorubicin, which allows efficient delocalization of π-electrons across the molecular framework[18]. Such stabilization of frontier molecular orbitals has been widely reported in computational studies of drug molecules and considered a key factor governing their electronic robustness and pharmacological stability.

The amphiphilic polymer exhibits a moderately high ionization potential (6.67 eV), indicating that the polymer backbone maintains substantial electronic stability while retaining limited electron-donating ability. This characteristic is desirable for polymeric drug carriers because stable electronic structures help maintain the structural integrity of the delivery matrix and minimize undesired redox reactions during circulation in biological environments[19,20]. Polymeric nanocarriers designed for drug delivery typically require such electronic stability to ensure compatibility with biological systems while still allowing interaction with drug molecules.

Interestingly, upon conjugation with doxil, the polymer-drug complex displays a significantly reduced ionization potential (5.84 eV). The decrease in IP indicates that the conjugated system requires less energy for electron removal, reflecting enhanced electronic reactivity and increased charge transfer capability between the polymer and the drug and it also leads to HOMO destabilization and enhanced electron availability for intermolecular interactions. This reduction suggests effective orbital overlap and electronic coupling between the polymeric carrier and the drug molecule, resulting in improved charge delocalization within the conjugate structure. Similar trends have been reported in computational studies where polymer-drug conjugation alters frontier molecular orbital distributions and enhances intermolecular electronic communication[15].

From a drug delivery perspective, the reduced ionization potential in the conjugated system may facilitate stronger molecular interactions, improved drug encapsulation, and enhanced responsiveness to stimuli, eg, pH, or enzymatic triggers where the formation of host-guest complexes results in lower ionization potentials. Due to the increased orbital delocalization and donor-acceptor interactions These electronic changes can promote more efficient drug loading and controlled release behavior in polymer-based nanocarriers, which are essential features of advanced drug delivery platforms. Furthermore, modulation of electronic properties through polymer conjugation is an important strategy in the rational design of prodrug and nanomedicine systems aimed at improving therapeutic performance[19]. Overall, the DFT-derived ionization potential results demonstrate that conjugation between the amphiphilic polymer and doxil. It significantly alters electronic structure of the polymer – drug system, thereby enhancing its responsiveness, and highlighting the importance of electronic descriptors in understanding and optimizing polymer-assisted drug delivery mechanisms.

Electron affinity (A) is a fundamental global reactivity descriptor derived from density functional theory (DFT) that quantifies the ability of a molecular system to accept an additional electron. Within conceptual density functional theory, molecules with higher EA values possess stronger electron-accepting capability and greater participation in intermolecular charge-transfer processes. The calculated EA values for the present systems follow the order: drug (5.31 eV) > polymer-drug conjugate (4.38 eV) > polymer (1.49 eV), indicating clear differences in the electron-accepting behavior of the three species. The relatively low EA value of the polymer suggests that its LUMO orbital is located at a higher energy level, making electron capture energetically unfavorable[16]. Such behavior is typical for polymeric drug carriers with weakly conjugated or saturated backbones, where localized frontier orbitals limit electrophilic activity. In drug delivery applications, this electronic inertness is beneficial because it allows the polymer matrix to act as a stable scaffold that protects the therapeutic molecule while minimizing unwanted redox interactions during circulation.

In contrast, the significantly larger EA value of the drug reflects a stronger ability to accept electrons, which had attributed to the electronic structure of doxorubicin. The anthracycline framework of doxorubicin contains conjugated aromatic rings and multiple carbonyl groups capable of stabilizing additional electron density through resonance delocalization. These structural features lower the LUMO energy and increase electrophilicity, enabling the drug to participate effectively in donor-acceptor interactions with surrounding molecules. Molecules possessing high electron affinity are more likely to engage in charge-transfer interactions with electron-rich species, a property that strongly influences molecular recognition and adsorption processes in drug-carrier systems[19]. Previous computational investigations of drug adsorption on nanomaterials and polymer carriers have similarly shown that therapeutic molecules often behave as electron-accepting centers during complex formation, thereby stabilizing supramolecular assemblies through partial charge transfer.

The polymer-drug conjugate displays an intermediate EA value of 4.38 eV, which indicates a redistribution of frontier molecular orbital energies following the interaction between the polymer carrier and the drug molecule. When conjugation occurs, orbital mixing and partial electron delocalization can take place across the host-guest interface, modifying both HOMO and LUMO energy levels. As a result, the LUMO of the complex becomes more stable than that of the isolated polymer while remaining slightly higher than that of the free drug. Such intermediate EA values are widely interpreted as evidence of partial charge transfer and electronic coupling between interacting fragments[11]. This donor-acceptor interaction suggests that electron density transfer from the polymer backbone toward the drug molecule, producing a hybrid electronic structure that balances stability with electronic responsiveness. In polymer-based drug delivery systems, such balanced electronic behavior is desirable because it promotes stable drug loading while maintaining the potential for controlled release under specific environmental conditions. Overall, the EA trend observed in this study demonstrates that conjugation significantly modifies the electronic structure of the polymer-drug system, providing molecular-level evidence for electronic interaction, charge redistribution, and enhanced electronic adaptability in the hybrid complex.

3.3. Chemical hardness and chemical softness

Chemical hardness (η) is a central global descriptor within conceptual density functional theory (DFT) that characterizes the resistance of a molecular system to deformation of its electron density during chemical interaction and reflects the intrinsic stability of a molecule and its susceptibility to charge transfer. Systems with large hardness values typically exhibit low polarizability and high resistance to electronic perturbations, whereas molecules with smaller hardness values are considered "soft," meaning their electron clouds can more readily reorganize during intermolecular interactions. For molecular assemblies such as drug-carrier systems, hardness therefore provides valuable insight into the balance between stability and reactivity that governs complex formation and molecular recognition. In the present system, the calculated hardness values follow the trend polymer (2.59 eV) > doxorubicin (1.05 eV) > polymer-doxorubicin conjugate (0.74 eV), indicating a progressive decrease in resistance to charge redistribution as the system evolves from the isolated carrier to the hybrid complex. Such analyses are widely used within conceptual DFT frameworks to interpret the electronic structure and reactivity patterns of molecular systems in chemical and pharmaceutical contexts[18].

The relatively high hardness of the polymer (2.59 eV) suggests that the carrier possesses a rigid electronic structure with a substantial separation between its frontier molecular orbitals. Polymers used in drug delivery often exhibit such behavior because their electronic structures are dominated by localized orbitals and limited π-conjugation along the backbone. Consequently, the polymer matrix behaves as an electronically stable scaffold that resists charge transfer and maintains structural integrity in complex biological environments. In contrast, the hardness of doxorubicin (1.05 eV) is considerably lower, reflecting a more polarizable electronic structure that can respond readily to surrounding chemical environments. The anthracycline framework of doxorubicin contains multiple aromatic rings and carbonyl groups that enable electron delocalization and facilitate redistribution of electron density. This electronic flexibility is typical for bioactive molecules whose function depends on interactions with biomolecular targets or carrier systems. Computational investigations of drug-carrier assemblies frequently report similar trends in which the active pharmaceutical ingredient displays lower hardness than the supporting carrier material, reflecting the drug's role as the electronically adaptable component of the system[15].

The most significant feature of the present results is the further reduction of hardness to 0.74 eV upon formation of the polymer-doxorubicin conjugate. The emergence of a softer electronic environment in the complex suggests that conjugation promotes electronic coupling between the polymer backbone and the drug molecule. Orbital interactions at the interface can lead to partial delocalization of electron density across the combined system, reducing the energy required for electronic redistribution and thereby lowering the global hardness. Similar reductions in chemical hardness have been reported in theoretical studies of drug adsorption on nanomaterials and polymeric carriers, where enhanced electronic coupling is associated with stronger intermolecular interactions and improved adsorption stability[11]. From a functional perspective, the increased softness of the conjugate implies greater electronic adaptability, which may facilitate charge redistribution under physiological stimuli and contribute to controlled drug release mechanisms. The hardness trend therefore provides strong evidence for effective electronic interaction between the polymer and doxorubicin components, demonstrating that the conjugation process produces a hybrid system whose electronic properties are distinct from those of its individual constituents and whose stability-reactivity balance is well suited for polymer-assisted drug delivery applications[8].

Chemical softness (S) is an important global reactivity descriptor in DFT framework. It describes the capacity of a molecular system to undergo redistribution of its electron density during chemical interactions and therefore systems with larger softness values exhibit greater electronic polarizability and enhanced susceptibility to charge transfer processes. In theoretical studies of molecular assemblies, softness provides insight into the electronic adaptability of molecules and their ability to participate in donor-acceptor interactions, intermolecular bonding, and electronic coupling phenomena. It also reflects how easily the electron cloud of a molecule can be perturbed to interpret the reactivity and stability of complex molecular systems. Conceptual DFT studies have consistently demonstrated that molecules with higher softness values tend to show stronger charge-transfer interactions and improved electronic communication with surrounding molecular environments[16].

The calculated softness values for the present system follow the trend: polymer (0.19 eV^{-1}) < doxil (0.48 eV^{-1}) < polymer-doxil conjugate (0.68 eV^{-1}), revealing a gradual increase in electronic flexibility from the isolated carrier to the hybrid complex. The relatively small softness value obtained for the polymer indicates that the polymer backbone possesses a comparatively rigid electronic structure with limited ability to redistribute electron density. Such behavior is typical for polymeric drug carriers whose frontier molecular orbitals are often localized and whose structures contain limited π-conjugation. Consequently, the polymer framework behaves as an electronically stable scaffold capable of maintaining structural integrity during drug transport and storage. In contrast, the anticancer drug doxorubicin exhibits a substantially higher softness value (0.48 eV^{-1}), reflecting greater electronic polarizability and an increased tendency to participate in intermolecular charge-transfer interactions. The anthracycline framework of doxorubicin contains extended aromatic π-systems and multiple heteroatom-containing functional groups that facilitate electron delocalization and enhance the ability of the molecule to redistribute charge during chemical interactions[14]. Similar electronic characteristics have been reported for many bioactive pharmaceutical molecules, which often display moderate softness values due to their conjugated structures and functional group diversity.

The polymer-doxil conjugate exhibits the highest softness value (0.68 eV^{-1}), indicating that complex formation significantly increases the electronic adaptability of the system. A rise in softness upon conjugation is being interpreted as evidence of enhanced electronic coupling between the interacting fragments. Orbital overlap between the polymer backbone and the drug molecule can promote partial delocalization of electron density across the interface, thereby increasing polarizability and facilitating charge-transfer interactions within the hybrid system. Such electronic "softening" is frequently observed in DFT investigations of drug-carrier complexes, where the formation of supramolecular assemblies modifies frontier orbital energies and enhances the electronic communicative interactions between host and guest molecules[4,18]. From a pharmaceutical perspective, the increased softness of the conjugate suggests a more responsive electronic environment capable of adapting to external stimuli such as solvent effects, pH variation, or biological interactions. Consequently, the softness trend observed in this study supports the formation of an electronically coupled polymer-drug complex and highlights the role of conceptual DFT descriptors in elucidating the stability, reactivity, and functional behavior of advanced polymer-based drug delivery systems.

3.4. Electronegativity and chemical potential

Electronegativity (χ) is a central global descriptor in conceptual DFT that reflects the tendency of a molecular system to attract and retain electron density during chemical interactions. Consequently, electronegativity provides valuable information about electron-transfer processes, donor-acceptor interactions, and molecular stability. Because electron transfer often drives intermolecular binding and adsorption processes, electronegativity has become a useful theoretical parameter for predicting interaction patterns and reactivity trends in pharmaceutical nanomaterials and supramolecular drug formulations[15].

The calculated electronegativity values obtained in this study follow the order doxorubicin (6.36 eV) > polymer-doxorubicin conjugate (5.12 eV) > polymer (4.08 eV), indicating notable differences in the electron-attracting capability of the three systems. The relatively low electronegativity of the polymer suggests a weaker tendency to attract electron density, which is consistent with the electronic characteristics of many polymeric drug carriers. Such materials typically possess localized frontier molecular orbitals and limited π-conjugation along the backbone, leading to moderate electron-withdrawing capability and enhanced electronic stability. In drug-delivery applications this property is advantageous because the polymer matrix primarily acts as a structurally stable scaffold that transports the therapeutic agent without strongly perturbing its intrinsic electronic characteristics. Previous computational studies have similarly reported that polymer carriers generally display lower electronegativity values than active pharmaceutical molecules, reflecting their comparatively inert electronic character and their role as electron-donating environments during drug-carrier interaction[16,19].

In contrast, the significantly higher electronegativity calculated for doxorubicin (6.36 eV) indicates a strong tendency to attract electron density. This is due to the electron-deficient anthracycline framework of the molecule, which contains conjugated aromatic rings and several carbonyl and hydroxyl groups capable of stabilizing incoming electron density through resonance delocalization. Molecules with high electronegativity commonly behave as electron-accepting species in donor-acceptor interactions, a property that is consistent with the known ability of doxorubicin to interact with biomolecular targets such as DNA through π–π stacking and electrostatic interactions. Conceptual DFT descriptors are frequently used in drug-design studies to rationalize such interaction mechanisms and to predict how electronic properties influence molecular recognition and binding processes[14].

Upon conjugation, the polymer-doxorubicin complex exhibits an intermediate electronegativity value of 5.12 eV, indicating that electronic redistribution occurs between the polymer backbone and the drug molecule. Such a shift suggests partial charge transfer and electronic coupling within the hybrid system, producing a new electronic environment in which electron density is shared across the polymer-drug interface. In conceptual DFT, intermediate electronegativity values are often interpreted as evidence of orbital interaction and charge delocalization between the interacting components. This electronic “equalization” can stabilize the complex while simultaneously enhancing intermolecular compatibility between the carrier and the drug. Similar electronic modulation has been reported in theoretical studies of polymer-drug conjugates and nanocarrier systems, where differences in electronegativity between the host and guest molecules determine the direction of charge transfer and influence adsorption stability, binding strength, and drug-release behavior[15]. Overall, the electronegativity trend observed here indicates that doxorubicin acts as the primary electron-accepting component while the polymer provides structural support and moderate electron donation, leading to an electronically balanced conjugate that may enhance drug-carrier compatibility and improve the efficiency of polymer-assisted drug-delivery systems.

Chemical potential (μ) is a fundamental global descriptor within conceptual DFT. It describes the tendency of a molecule to either donate or accept electrons during chemical interactions. Physically, the chemical potential represents the escaping tendency of electrons from a molecular system and therefore provides important insight into charge-transfer processes. Molecules with more negative μ values generally display stronger electron-accepting character, whereas less negative values indicate a greater ability to donate electron density. Because of this relationship, chemical potential is widely used in conceptual DFT analyses to interpret electron transfer, intermolecular interactions, and electronic stabilization in molecular complexes, particularly in studies of drug-carrier systems and nanostructured delivery platforms[17,19].

The calculated chemical potential values in the present study follow the order doxorubicin (−6.36 eV) < polymer-doxorubicin conjugate (−5.12 eV) < polymer (−4.08 eV), indicating clear differences in the electron-attracting capability of the three systems. The relatively less negative chemical potential of the polymer suggests a weaker tendency to attract electron density compared with the drug molecule. Such behavior is characteristic of many polymeric carrier materials whose electronic structures are relatively stable and less reactive due to localized frontier orbitals and limited conjugation. In polymer-based drug delivery platforms, the carrier typically functions as a structural matrix that stabilizes the therapeutic molecule while enabling controlled interactions with the surrounding environment. Computational investigations of polymer-drug delivery systems have similarly reported that polymeric carriers often exhibit higher chemical potential values than the associated drug molecules, reflecting their comparatively electron-donating character and structural stability[16].

In contrast, the anticancer drug doxorubicin exhibits the most negative chemical potential (−6.36 eV), indicating a stronger tendency to attract electron density and behave as an electron-accepting species during intermolecular interactions. This electronic behavior can mainly be attributed to the anthracycline framework of doxorubicin, which contains an extended aromatic π-system together with several carbonyl and hydroxyl functional groups capable of stabilizing additional electron density through resonance delocalization. Molecules with highly negative chemical potential values are generally associated with enhanced electrophilic character and strong interaction potential with electron-donating partners. These electronic characteristics are consistent with the known ability of doxorubicin to interact with biomolecules through π–π stacking and electrostatic interactions, processes that are often rationalized using conceptual DFT descriptors such as chemical potential and electronegativity in theoretical drug-design studies[11,16].

Upon conjugation, the polymer-doxorubicin complex exhibits an intermediate chemical potential value of −5.12 eV, suggesting that electronic coupling occurs between the polymer backbone and the drug molecule. The shift toward an intermediate μ value indicates redistribution of electron density across the conjugated system, leading to partial charge transfer between the interacting molecular fragments. Within conceptual DFT theory, this phenomenon is consistent with the electronegativity equalization principle, according to which interacting molecules adjust their electron densities until a common electronic potential is established. Consequently, the conjugate adopts a balanced electronic state that is more stable than the isolated polymer yet less electrophilic than the free drug. Similar electronic modulation has been observed in computational studies of drug-carrier complexes, where intermediate chemical potential values reflect improved electronic compatibility between host and guest molecules and contribute to enhanced stability and controlled drug-release behavior[14,18]. Overall, the chemical potential analysis indicates that electron density is likely transferred from the polymer toward the drug during complex formation, producing an electronically stabilized polymer-doxorubicin assembly that is favorable for advanced polymer-assisted drug delivery systems.

3.5. Electrophilicity index and hydrophobicity

The electrophilicity index (ω) is a fundamental global descriptor within conceptual DFT that quantifies the ability of a molecular system to accept electron density from its surroundings. Because this descriptor integrates both the electron - attracting tendency of molecules, and also its resistance to electronic cloud deformation or distortions, it provides a comprehensive measure of electrophilic reactivity. In theoretical chemistry and materials science, electrophilicity has become a widely used parameter for interpreting molecular stability, charge-transfer processes, and intermolecular interactions in complex systems. In particular, conceptual DFT descriptors have been extensively applied to understand the electronic behavior of pharmaceutical molecules and polymer-based nanocarriers involved in drug delivery processes[17,19].

The calculated electrophilicity values in the present study follow the order doxorubicin (19.26 eV) > polymer-doxorubicin conjugate (17.83 eV) >> polymer (3.21 eV), demonstrating substantial differences in the electron-accepting capability of the investigated systems. The comparatively low electrophilicity value obtained for the polymer indicates that the polymer backbone possesses weak electrophilic character and a limited ability to stabilize additional electron density. Such behavior is consistent with the electronic properties of many polymeric drug carriers, which are typically designed to function as chemically stable frameworks rather than highly reactive electrophilic species. Their relatively low electrophilicity contributes to the structural stability of the carrier matrix and prevents unwanted side reactions during drug transport and storage. Computational investigations of polymer-based delivery systems similarly report modest electrophilicity values for polymer frameworks, reflecting their role as electronically stable host materials capable of interacting with therapeutic molecules without significantly altering their intrinsic reactivity[16].

In contrast, the anticancer drug doxorubicin exhibits a remarkably high electrophilicity value (19.26 eV), indicating a strong ability to accept electron density during molecular interactions. This behavior arises primarily from the electronic structure of the anthracycline molecule, which contains multiple conjugated aromatic rings together with carbonyl and hydroxyl functional groups that can stabilize incoming electron density through resonance delocalization. Molecules with high electrophilicity indices typically display strong charge-transfer capability and enhanced affinity toward electron-rich environments. These electronic characteristics help explain the well-known ability of doxorubicin to interact strongly with biomolecular targets such as DNA and proteins through π–π stacking and electrostatic interactions, which are central to its anticancer activity. Conceptual DFT descriptors such as electrophilicity are therefore frequently employed in theoretical drug-design studies to rationalize molecular recognition and interaction mechanisms in pharmaceutical systems[14,18].

The electrophilicity value of the polymer-doxorubicin conjugate (17.83 eV) remains significantly higher than that of the polymer but slightly lower than that of the free drug, indicating that conjugation moderates the intrinsic electrophilic character of doxorubicin while preserving its strong electron-accepting capability. The slight reduction in ω relative to the free drug suggests a partial redistribution of electron density between the polymer backbone, and the drug molecule, leading to improved electronic stabilization of the hybrid system. Such intermediate electrophilicity values are commonly observed in theoretical investigations of polymer-drug and nanocarrier-drug complexes, where conjugation produces balanced electronic interactions between the carrier and the therapeutic molecule. From a drug-delivery perspective, this moderated electrophilic character is advantageous because it supports stable drug loading while still enabling the charge-transfer interactions required for molecular recognition and controlled release processes[11]. Consequently, the electrophilicity trend observed in this study provides important molecular-level insight into the electronic stabilization and interaction mechanisms governing the formation of the polymer-doxorubicin conjugate system[15].

To increase hydrophobicity of polymer molecules, number of methylene groups between benzene ring and pyrrole ring are increased (Figure 3). More is the number of the methylene groups, more in hydrophobicity behaviour in nature and it in turn rises the bioavailability of polymer and medicine in human body. Less is the hydrophobic, the polymer is excreted faster in urine. From DFT calculations, hydrophobicity increases with increase in HOMO – LUMO gaps. Also, higher gaps generally indicate lower chemical reactivity, higher stability, and weaker intermolecular interactions with water. Larger gaps are associated with increased saturated character, whereas enhanced conjugation (lower band gap) often increases polarity and electronic interaction[17].

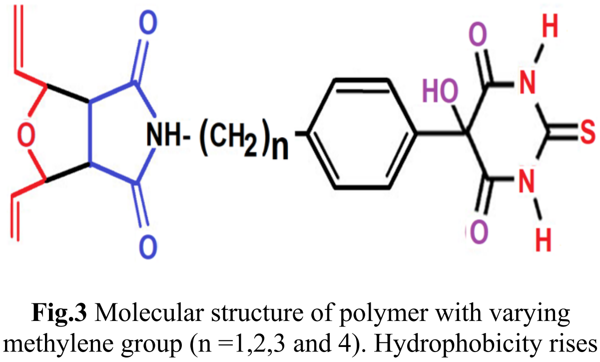

Fig.3 Molecular structure of polymer with varying methylene group (n =1,2,3 and 4). Hydrophobicity rises with increase in number of methylene group between pyrrole ring and benzene ring in the polymer molecule.

4. CONCLUSIONS

In this modeling research, drug encapsulation in laboratory made polymer, and rate of drug release from polymer was qualitatively and semi- quantitatively analysed using DFT data obtained from Gaussian 16 software. Chemical reactivity was analysed using descriptors such as HOMO and LUMO energies, and chemical reactivity parameters. This evaluation helps understand molecular stability and charge-transfer behavior. The results showed that the polymer-drug conjugate exhibited a significantly reduced band gap of 1.47 eV compared with the isolated polymer (5.18 eV) and the free drug (2.1 eV), this reduction suggests stronger electronic coupling and enhanced intermolecular charge-transfer interactions after conjugation. Furthermore, the conjugate displayed increased chemical softness of 0.19 eV^{-1} of the polymer to 0.68 eV^{-1} of the polymer-drug conjugate and moderate electrophilicity of the polymer-drug conjugate (17.83 eV), indicating better electronic adaptability by reduction in the chemical hardness in polymer from 2.59 eV to 0.74 eV in the conjugate that may support efficient drug loading and controlled release. Also, the increase in electronegativity from 4.08 eV of the polymer to 6.36 eV in the drug with conjugate having 5.12 eV indicates that doxorubicin acts as the primary electron-accepting component while the polymer provides structural support and moderate electron donation, leading to an electronically balanced conjugate that may enhance drug-carrier compatibility and improve the efficiency of polymer-assisted drug-delivery systems. These findings emphasize that polymer-drug conjugation changes electronic properties and improves interaction capability. This provides valuable theoretical support for the design of advanced polymer-based nanocarriers for anticancer drug delivery. These outputs support earlier experiments done by us[4]. When number of methylene group is increased, hydrophobicity rises making improved bioavailabilty of polymer and in turn drug.

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Conflict of Interests

There is no conflict of interest in this work.

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All research output data is given in Table and Figures.

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