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Investigating variability in PLGA monomers: A comparative study of electronic properties and their role in drug delivery systems

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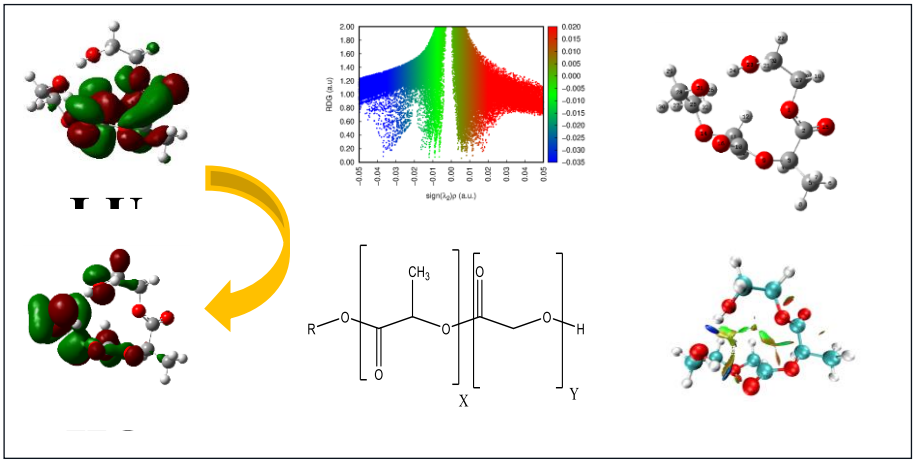
HIGHLIGHTS

- This study uses computational methods to explore how monomer arrangement and PEG addition influence PLGA's properties for drug delivery.
- DFT calculations reveal that PEG reduces the energy gap and enhances dipole moments, improving nanoparticle stability.
- Certain configurations, like XYXX-PEG-XYXX, show promise as drug carriers.
- Noncovalent interactions also suggest potential for sustained release of therapeutics.

GRAPHICAL ABSTRACT



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ABSTRACT

PLGA (poly(lactic-co-glycolic) acid) is a biodegradable copolymer commonly used in drug delivery. It is composed of monomers X and Y, which influence its physical and chemical properties. Incorporating hydrophilic polymers like polyethylene glycol (PEG) into PLGA enhances the circulation half-life of nanoparticles. This study employs computational methods to investigate how variations in the number and arrangement of monomers X and Y, as well as PEG integration, affect PLGA's properties. Using Density Functional Theory (DFT) calculations, we analyze several physicochemical characteristics, including the energy gap and dipole moment. Our results show that PEG incorporation reduces the energy gap, with configurations like XYXX-PEG-XYXX and XXYYY emerging as promising drug carrier candidates. Furthermore, an increased ratio of X to Y generally elevates the dipole moment, particularly with PEG present, which improves the dipole moment further. Noncovalent interaction analysis indicates that certain PLGA monomers may exhibit beneficial van der Waals interactions, enhancing the sustained release of therapeutic agents.

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1. Introduction

Nanotechnology encompasses the fields of science and engineering that leverage phenomena occurring at the nanoscale to design, characterize, fabricate, and apply materials, structures, devices, and systems [1]. This innovative field has the potential to revolutionize medical research and pave the way for human enhancement.

It offers promising opportunities in diagnostics, therapeutics, and preventive care [2-4]. Such advanced technologies enable targeted modifications within the body, addressing various health issues. The nano medications employed in this approach demonstrate improved bioavailability, reduced side effects, and enhanced absorption of therapeutic compounds [5, 6]. Biomedical research is progressing through innovative drug delivery methods that integrate conventional and engineered technologies, aimed at improving medication selectivity for specific cells and optimizing release rates.

These systems primarily utilize biodegradable and biocompatible polymers as delivery vehicles to effectively target therapeutic agents and vaccines. By ensuring controlled release, these drug delivery systems enhance the overall therapeutic efficacy of treatments [7]. Biodegradable polymers, particularly poly (lactic-co-glycolic acid) (PLGA), have been extensively studied for drug delivery and tissue engineering since their introduction nearly thirty years ago. PLGA, an FDA-approved polymer, is recognized for its mechanical strength and biocompatibility, making it effective for delivering drugs, proteins, and macromolecules such as DNA and RNA [8-10]. Among biodegradable polymers, PLGA stands out due to its clinical history, favorable degradation characteristics, and sustained drug release capabilities.

Recent studies indicate that PLGA can facilitate controlled drug release via implantation without the need for surgical intervention. By modulating factors such as molecular weight and drug concentration, the polymer-drug matrix can be optimized for specific dosage and release requirements [11-13]. Concerns regarding toxicity, dose dumping, variable release rates, and drug-polymer interactions underscore the necessity for thorough research on PLGA, a copolymer of polylactic acid (PLA) and polyglycolic acid (PGA).

Due to its minimal systemic toxicity and controllable degradation behavior, PLGA is widely utilized in biodegradable drug delivery systems. Its mechanical properties can be tailored for specific tissues, and the PLA-to-glycolic acid ratio governs the degradation rate, thereby enhancing its medical utility [14]. The structure of poly (lactic-co-glycolic acid) (PLGA) is illustrated in Scheme 1. As previously mentioned, PLGA consists of monomers X and Y, which differ in atom counts and structures. The arrangement of these monomers can vary, and they may also be substituted.

Modifying the number of monomers in the PLGA copolymer creates new polymers with distinct physical and chemical properties, which in turn exhibit varying structures and energies. Nanoparticles can be coated with molecules that form a hydrophilic layer on their surfaces, effectively concealing their inherent hydrophobic characteristics. A widely used agent for surface modification is polyethylene glycol (PEG), a hydrophilic and non-ionic polymer.

The incorporation of PEG can significantly enhance the circulation half-life of nanoparticles by several folds and demonstrates excellent biocompatibility. When added to a PLGA formulation, ethylene glycol results in a copolymer that typically possesses low viscosity and fluidity at low temperatures. However, upon reaching physiological temperatures, this copolymer can transition into a gel with high viscosity. PEG can be attached to the polymer in various configurations, and we have briefly reviewed several types of these linkages [15].

Consequently, this study presents a comprehensive comparative analysis of the electronic properties, dipole moments, and noncovalent interaction (NCI) properties of PLGA monomers with varying quantities and placements, with the results reported herein. The findings and data from this study may prove beneficial for utilizing this polymer as a drug carrier.

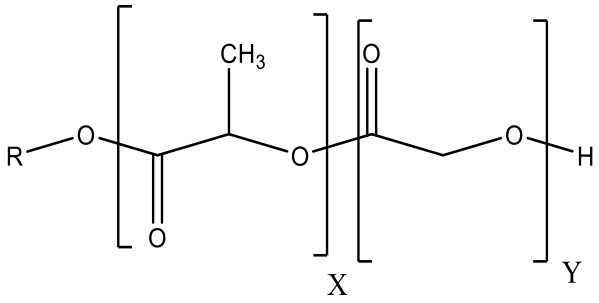


Figure 1 The structure of polylactic-co-glycolic acid (PLGA).X: PLA; Y: PGA

2. Computational details

The geometries of the ground state for the species under investigation were optimized using the hybrid density functional method B3LYP [16-18].

This method has been shown to provide accurate geometries across a wide range of systems. All computations were performed with the 6-31G(d,p) basis set within the Gaussian 09 software suite [7, 19]. Harmonic vibrational frequencies were computed using the same theoretical framework to confirm that all stationary points on the potential energy surface are local minima. The nature of the non-covalent interactions (NCI) between the proton donor and acceptor pairs in the PLGA monomers was examined using Multiwfn software [20] and Visual Molecular Dynamics (VMD) version 1.9.4 [21, 22]. The three-dimensional (3D) isosurface maps of the PLGA monomers were visualized with the assistance of Gnuplot version 5.5-git [23].

3. Results and discussion

3.1. Frontier molecular orbitals

The molecular orbital theory encompasses the concept of frontier orbital control. According to this concept, the most significant interactions occur between a specific pair of orbitals, namely the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO). In molecular orbital theory, the interaction between orbitals depends on their relative energy levels; specifically, the closer they are in energy, the stronger the interaction between them. Furthermore, as the energy gap between the frontier orbitals decreases, the overlap of their wave functions in response to an external field increases, leading to a more substantial mutual interaction [24].

The difference between the HOMO and the LUMO is commonly referred to as the energy gap ($E_{GAP} = E_{LUMO} - E_{HOMO}$), which is a crucial characteristic determining properties associated with electronic transitions. The energies of the outermost molecular orbitals, including HOMO and LUMO, along with the energy gap values, are fundamental parameters in establishing the conductivity of molecules.

The reactivity of softer chemical species, defined as those with smaller energy gaps, is generally greater than that of harder species. The energy values of the HOMO and LUMO molecular orbitals, as well as the band gap, have been calculated for various PLGA compounds examined in this study, with the results presented in Tables 1 and 2.

This section focuses on the energy differences between HOMO and LUMO in PLGA compounds with varying numbers of monomers and the impact of changes in the positions of these monomers. It is generally understood that a smaller energy gap corresponds to increased reactivity.

Table 1 Frontier molecular orbital energy (E_{HOMO} and E_{LUMO} in eV), energy gap (E_g in eV), for PLGA and its monomers calculated using the B3LYP/6-31G(d,p) level of theory in the gas phase.

	E_{HOMO}	E_{LUMO}	E_{gap}
XY	-7.467	-0.572	6.895
XXY	-7.037	-0.577	6.460
XYX	-7.057	-0.919	6.138
YXX	-7.459	-0.672	6.787
XXYY	-7.491	-1.072	6.419
XYYX	-7.253	-1.086	6.168
XYXY	-7.252	-1.025	6.227
YXXY	-7.612	-0.964	6.648
XXYX	-7.744	-0.965	6.779
XYXX	-7.191	-0.721	6.469
YXXX	-7.428	-0.925	6.503
XXXY	-7.442	-1.220	6.223
XXYYY	-6.978	-1.341	5.637
YX	-7.441	-0.318	7.122
YYX	-7.534	-1.236	6.298
YXY	-7.368	-1.174	6.194
YYYX	-7.380	-1.499	5.881
YYXY	-7.520	-1.228	6.292
YXYY	-7.558	-1.468	6.089

Table 2 Frontier molecular orbital energy (E_{HOMO} and E_{LUMO} in eV), energy gap (E_g in eV), for PLGA and its monomers with increasing polyethylene glycol (E_g) calculated using the B3LYP/6-31G(d,p) level of theory in the gas phase.

	E_{HOMO}	E_{LUMO}	$E_{gap.}$
XY-EG-XY	-7.224	-0.918	6.305
EG-XY-EG	-7.049	-0.328	6.721
EG-XXYY-EG	-7.205	-1.205	6.000
EG-XYXY-EG	-7.109	-1.345	5.764
EG-XYYX-EG	-6.734	-0.937	5.798
EG-XXXY-EG	-6.891	-1.185	5.706
EG-XXYX-EG	-6.988	-0.926	6.061
EG-XYXX-EG	-7.117	-1.007	6.110
EG-YXXX-EG	-7.290	-1.041	6.249
XXXY-EG-XXXY	-7.071	-1.177	5.894
XXYX-EG-XXYX	-7.528	-1.179	6.349
XYXX-EG-XYXX	-7.177	-1.497	5.681
YXXX-EG-YXXX	-6.991	-1.277	5.714

Based on the results presented in Table 1, the energy gap values of PLGA compounds vary with changes in the ratio of lactic acid (X) to glycolic acid (Y) and alterations in their connectivity positions. Among the compounds examined, the structures XXYYY and YYYX exhibit the lowest energy gaps of 5.637 eV and 5.881 eV, respectively, while the structures YX and XY display the highest energy gaps of 7.122 eV and 6.895 eV, respectively. This section examines the stability and reactivity of PLGA compounds concerning the effects of ethylene glycol (EG) attachment at various positions. Generally, the addition of EG to these structures alters the energy gap, with the extent of this change depending on the specific attachment position of EG. According to the data presented in Table 2, it is evident that attaching EG to the PLGA structures at different positions results in a reduction of the energy gap for these compounds.

This reduction can be interpreted as a decrease in stability, leading to increased reactivity compared to the original compounds. The decrease in the energy gap can be attributed to an increase in E_{LUMO}. Among the studied compounds, the structures EG-XY-EG and XYXX-EG-XYXX exhibit the highest and lowest energy gaps, respectively. The XYXX-EG-XYXX and XXYYY structures, which possess low energy gaps, demonstrate a high potential for effective interactions with drugs, suggesting their suitability as candidates for drug delivery or carrier applications. The electron density distribution diagrams for the HOMO and LUMO of selected PLGA and PLGA-EG structures are shown in Figure 1

The electron density distributions for the HOMO and LUMO of selected PLGA compounds are illustrated in Figure 1. The results indicate that altering the positions of the monomers X and Y leads to variations in the electron distribution of the HOMO and LUMO, which affects their respective densities. Thus, changes in the number and positions of these monomers significantly impact the electron distribution of the frontier orbitals. Regions of the HOMO electron density distribution represent areas rich in electrons, while regions of the LUMO electron density distribution correspond to areas that are electron-deficient.

3.2. Chemical reactivity

The amount of energy exchanged during the process of adding an electron to a neutral gaseous atom in its ground state is referred to as electron affinity. Electron affinity is defined as $A=-E_{LUMO}$. In contrast, ionization energy pertains to the process of generating a positive ion from a neutral atom through the loss of an electron, represented as $I=-E_{HOMO}$. The relationship between electron affinity and ionization energy is associated with the process whereby a neutral atom forms a negative ion by gaining an electron [25]. Chemical hardness can be understood as the measure of a molecule's resistance to charge transfer, approximately equal to half of the energy gap [26]. It is introduced by the equation (1):

$$\eta = \frac{(E_{LUMO} - E_{HOMO})}{2} \quad (1)$$

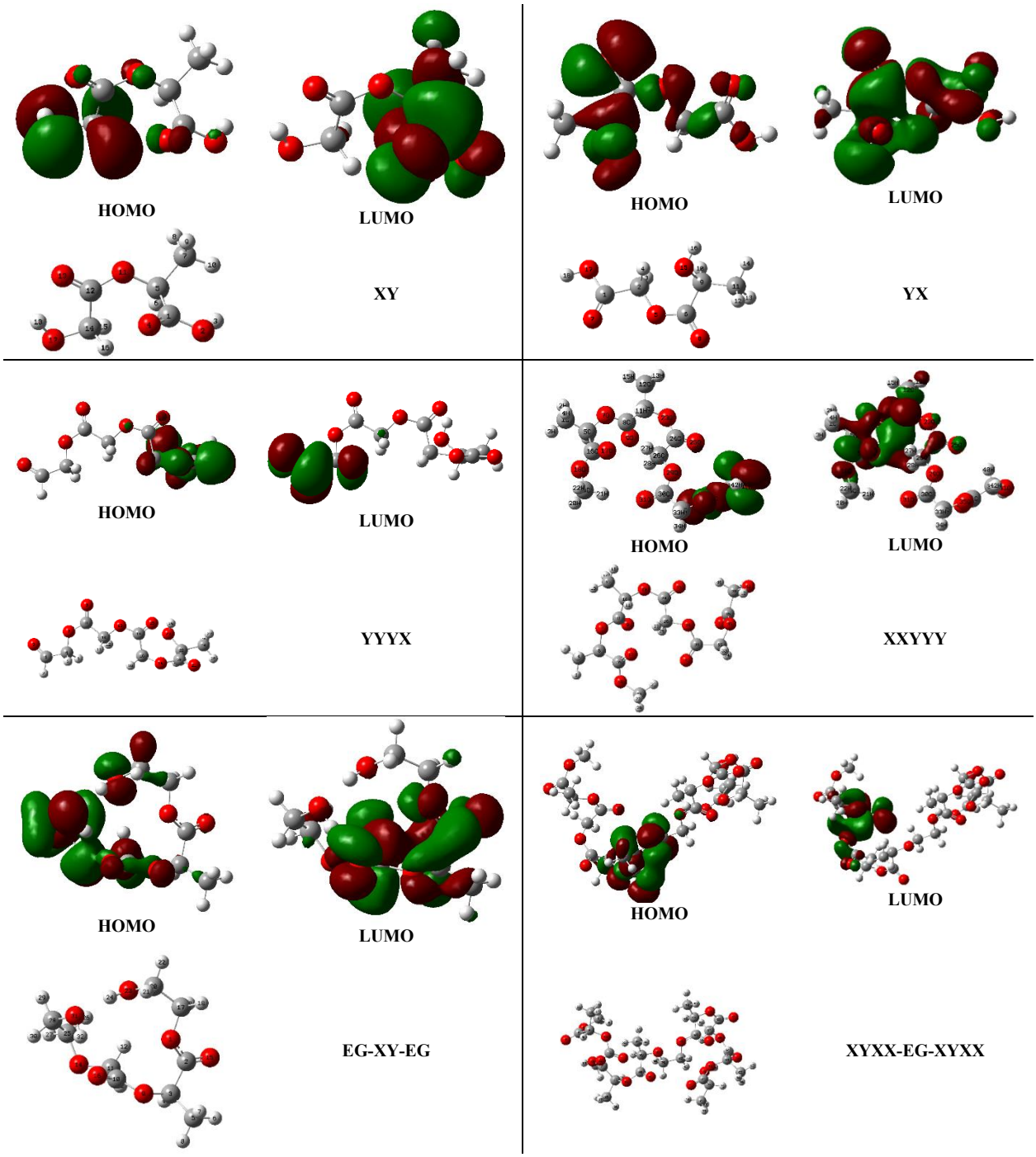


Figure 1 The HOMO and LUMO of some PLGA monomers.

According to the principle of maximum hardness, as the energy gap between the HOMO and LUMO orbitals increases, the chemical hardness also increases.

Reactivity is higher in softer chemical species, defined as those with smaller energy gaps compared to those of harder species. The concept of electronic chemical potential is closely related to work function, Fermi level, electronegativity, and ionization potential. Occasionally, the chemical potential of an atom is referred to as the electronegativity of the atom. Similarly, the equilibrium chemical potential is termed equilibrium electronegativity. This concept arises from Mulliken's definition of electronegativity, which integrates the concepts of ionization energy and electron affinity into the notion of electronegativity [27]. The magnitude of the chemical potential serves as a metric for the extent of electron transfer from a molecule with higher electronegativity to one with lower electronegativity, as expressed in Equation (2)

$$\mu = \frac{(E_{HOMO} + E_{LUMO})}{2} \quad (2)$$

Robert Parr developed a method for calculating the index of electron affinity, which indicates the stability of a molecule when it acquires an electron from its environment. [27], defined by Equation (3):

$$\omega = \frac{\mu^2}{2\eta} \quad (3)$$

To investigate the electronic parameters related to PLGA compounds, the ionization energy, electron affinity, chemical hardness, electronic chemical potential, and electron affinity index were calculated and reported in Tables 3 and 4. Comparison of the results in Table 3 indicates that as the ratio of lactic

Table 3 Calculation of chemical reactivity: ionization energy (I in eV), electron affinity (A in eV), chemical hardness (η in eV), electrophilicity (ω in eV), and chemical potential (μ in eV) for PLGA and Its monomers using the B3LYP/6-31G(d,p) level of theory in the gas phase.

	I	A	η	μ	ω
XY	7.4667	0.572	3.447	-4.019	27.845
XXY	7.038	0.577	3.230	-3.807	23.403
XYX	7.057	0.919	3.069	-3.988	24.401
YXX	7.459	0.672	3.394	-4.065	28.041
XXYY	7.491	1.072	3.210	-4.281	29.415
XYYX	7.253	1.086	3.084	-4.170	26.806
XYXY	7.252	1.025	3.113	-4.139	26.663
YXXY	7.612	0.964	3.324	-4.288	30.563
XXYX	7.744	0.965	3.390	-4.354	32.135
XYXX	7.191	0.721	3.235	-3.956	25.312
YXXX	7.428	0.925	3.251	-4.177	28.359
XXXY	7.442	1.220	3.111	-4.331	29.179
XXYYY	6.978	1.341	2.819	-4.160	24.385
YX	7.441	0.318	3.561	-3.879	26.798
YYX	7.5342	1.236	3.149	-4.385	30.277
YXY	7.368	1.174	3.097	-4.271	28.246
YYYX	7.3799	1.499	2.940	-4.439	28.976
YYXY	7.520	1.228	3.146	-4.374	30.092
YXYY	7.558	1.468	3.045	-4.513	31.004

Table 4 Calculation of chemical reactivity: ionization energy (I in eV), electron affinity (A in eV), chemical hardness (η in eV), electrophilicity (ω in eV), and chemical potential (μ in eV) for PLGA and **its monomers with increasing polyethylene glycol (EG)** using the B3LYP/6-31G(d,p) level of theory in the gas phase.

	I	A	η	μ	ω
XY-EG-XY	7.224	0.918	3.153	-4.071	26.125
EG-XY-EG	7.049	0.328	3.361	-3.688	22.859
EG-XXYY-EG	7.205	1.205	3.000	-4.205	26.528
EG-XYXY-EG	7.109	1.345	2.882	-4.227	25.749
EG-XYYX-EG	6.734	0.937	2.899	-3.836	21.324
EG-XXXY-EG	6.891	1.185	2.853	-4.038	23.265
EG-XXYX-EG	6.988	0.926	3.031	-3.957	23.725
EG-XYXX-EG	7.117	1.007	3.055	-4.062	25.205
EG-YXXX-EG	7.290	1.041	3.125	-4.165	27.101
XXXY-EG-XXXY	7.071	1.177	2.947	-4.124	25.060
XXYX-EG-XXYX	7.528	1.179	3.175	-4.353	30.082
XYXX-EG-XYXX	7.177	1.497	2.840	-4.337	26.711
YXXX-EG-YXXX	6.991	1.277	2.857	-4.134	24.416

acid (X) to glycolic acid (Y) increases, the chemical hardness of the PLGA compounds varies. In the PLGA compositions with a 2:1 ratio of lactic acid to glycolic acid, specifically in the compounds XXY, XYX, and YXX, the lowest chemical hardness of 3.06 eV is associated with the XYX structure. In contrast, in the PLGA compounds with a 3:1 ratio of lactic acid to glycolic acid, the compound XXXY exhibits the lowest chemical hardness of 3.11 eV compared to the structures XXYX, XYXX, and YXXX, indicating that it is more reactive than the other three compounds. These findings are consistent with the results regarding the energies of the frontier orbitals.

Moreover, the results from Table 3 demonstrate that as the proportion of glycolic acid (Y) relative to lactic acid (X) increases in the PLGA compounds, the overall chemical hardness decreases. Furthermore, the position of the monomers plays a significant role in determining chemical hardness.

The data reveal that at both 2:1 and 3:1 ratios, the lowest chemical hardness values of 3.10 eV and 2.94 eV correspond to the structures YXY and YYYX, respectively. Table 4 presents the values for chemical hardness, chemical potential, and the electron affinity index for PLGA compounds with EG attached at mid and terminal positions.

Although the analysis of the results in this table indicates a dependency of these quantities on the position of EG attachment, it does not demonstrate a clear trend. Similarly, the chemical hardness, chemical potential, and electron affinity index for various PLGA compounds have been calculated and reported in Tables 3 and 4. A comprehensive review indicates that as chemical hardness increases, both chemical potential and the electron affinity index decrease.

3.3 Dipole moment (Debay)

One of the essential properties of chemical bonds is polarity. When the electronegativities of two atoms forming a covalent bond are not equal, the bonding electrons shift according to the principle of electronegativity inequality. As a result, the centers of positive and negative charges within the bond become separated, causing the bond to behave as an electric dipole; such a bond is referred to as a polar bond. In multi-atomic molecules, polarity can be determined by the resultant dipole moment, indicating whether the molecule is polar or nonpolar. Given that most bonds exist on a spectrum between purely ionic and purely covalent, the dipole moment of a molecule is employed to characterize the nature of its bonds. A larger difference in electronegativity between atoms results in a more polar covalent bond, exhibiting greater interaction with its environment. The magnitude of the bond dipole is expressed as the dipole moment. The electric dipole moment is defined based on Equation (4):

$$\mu = Q \times r \quad (4)$$

where μ is the electric dipole moment, Q is the magnitude of two equal and oppositely charged particles, and r is the distance between the two charges. The electric dipole moment is a significant molecular property that provides important information about the geometric and electronic structure of the molecule [28]. The values of the electric dipole moment μ measured in Debye units for various compounds have been calculated and are presented in Figure 2.

Based on the results presented in diagram (a), when the ratio of glycolic acid (Y) to lactic acid (X) is 3:1, the dipole moments of the different monomer placements show minimal variation. The three compounds YYYX, YYXY, and YXY have electric dipole moments of 6.81, 6.86, and 6.89 Debye, respectively.

However, additional results indicate that for PLGA compounds with a 3:1 ratio of lactic acid to glycolic acid, significant changes in their dipole moments occur with varying monomer placements.

This variation is exemplified by the XYXX compound, which has a dipole moment of 5.83 Debye, compared to the XXYX compound with a dipole moment of 7.24 Debye. Diagram (a) also illustrates a scenario where the number of glycolic acid (Y) monomers is equal to that of lactic acid (X) monomers, with differences in their positions. The dipole moment of the XYYX compound, measuring 8.80 Debye, is greater than those of the other PLGA compounds with an equal number of monomers. The results indicate that as the proportion of lactic acid increases relative to glycolic acid, the dipole moment increases. Referring to diagram (b), the introduction of ethylene glycol into various positions of the identical PLGA compounds results in differing dipole moments. When ethylene glycol is positioned between identical PLGA monomers, the dipole moment is greater than when it is attached to the terminals of the PLGA compounds. For instance, the XY compound has a dipole moment of 6.37 Debye; however, when ethylene glycol is added to both ends (EG-XY-EG), the dipole moment decreases to 1.30 Debye. Conversely, when ethylene glycol is situated between the identical PLGA monomers (XY-EG-XY), the dipole moment increases to 9.24 Debye.

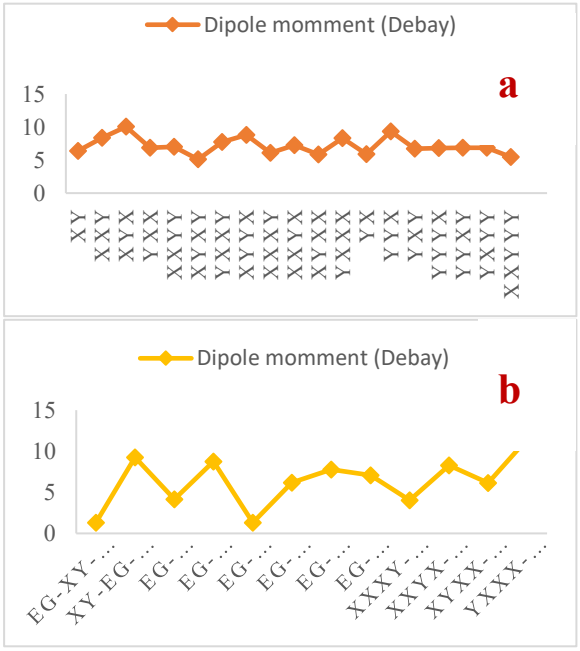


Figure 2 Graphical representation of the dipole moment (D in Debye) for (a) and (b) of PLGA monomers calculated using the B3LYP/6-31G(d,p) level of theory in the gas phase.

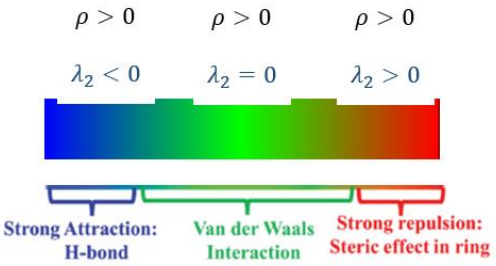
These results are consistent across other PLGA compounds, specifically those with a 3:1 ratio of lactic acid (X) to glycolic acid (Y). Comparing the electric dipole moments of the compounds in the presence and absence of ethylene glycol reveals that changes in dipole moments depend not only on monomer placement but also on the positioning of ethylene glycol. A comprehensive examination of the obtained data supports this conclusion. When ethylene glycol is situated between two PLGA compounds with identical monomers, a significant increase in the electric dipole moment is observed. This enhanced polarity may facilitate greater interactions between this segment of the PLGA compounds and therapeutic agents.

3.4. Noncovalent interactions (NCI) analysis

The noncovalent interaction (NCI) analysis provides valuable insights into the non-covalent interactions within a molecule. Using NCI plots, strong directional attractions associated with local atom-atom contacts, as well as regions of weak interactions, can be effectively identified. One key parameter in NCI analysis is the reduced density gradient (RDG), a dimensionless quantity that incorporates electron density and its first derivative. The RDG is mathematically defined as follows:

$$RDG(r) = \frac{1}{2(3\pi^2)^{1/3}} \frac{|\nabla_\rho(r)|}{\rho(r)^{4/3}}$$

In this equation, ρ(r) represents the electron density, |∇ρ(r)| denotes the magnitude of the electron density gradient, and $\lambda 2$ signifies the second eigenvalue of the electron density Hessian matrix, indicating the type of bonding present [29]. In the present study, several PLGA compounds exhibiting notable electronic properties are presented, as illustrated in Figure 3.



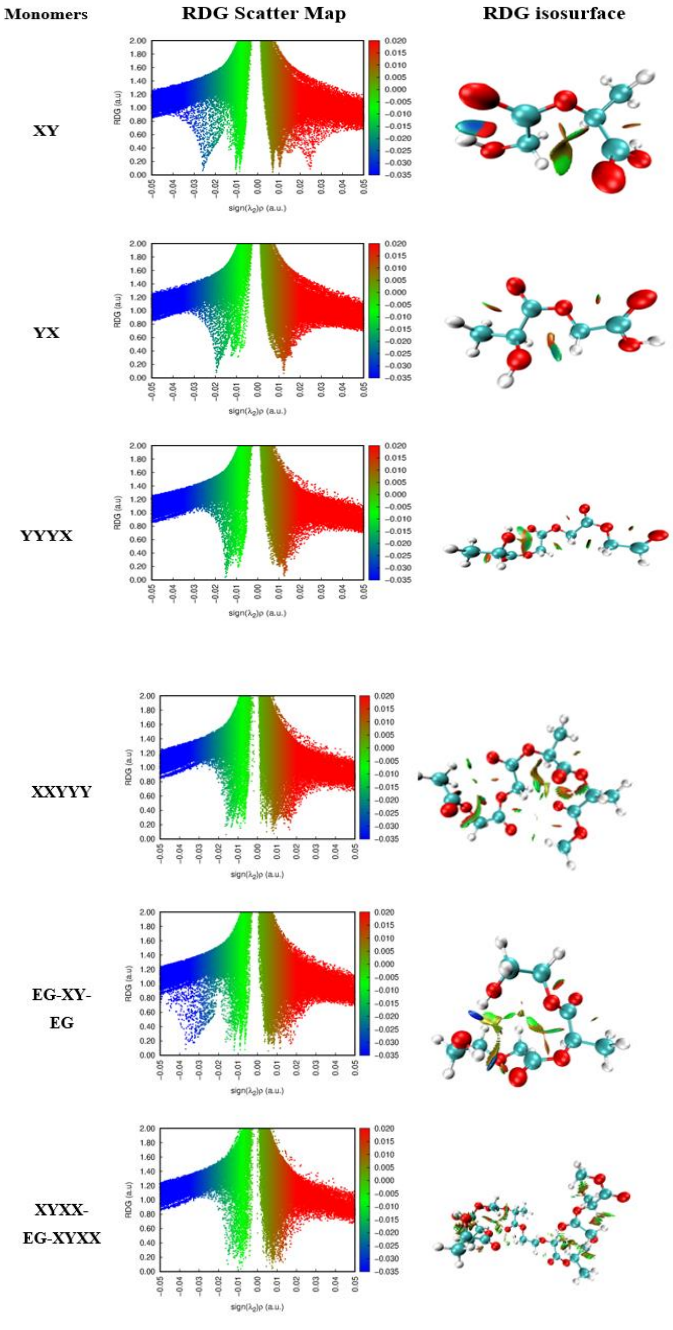


Figure 3 The RDG scatter maps, RDG isosurfaces of PLGA monomers structures.

This analysis not only elucidates the nature of non-covalent interactions in these compounds but also enhances our understanding of their chemical behavior and potential applications. Statistical information regarding the nature and strength of molecular interactions can be derived from the analysis of the Reduced Density Gradient (RDG) in conjunction with the sign of the parameter (λ2)ρ. The sign of (λ2)ρ plays a crucial role in characterizing these interactions. Specifically, a positive value of (λ2)ρ > 0 indicates a repulsive interaction (anti-bonding), while a negative value (λ2)ρ < 0 signifies an attractive interaction (bonding). Furthermore, a value of (λ2)ρ that is approximately zero typically corresponds to van der Waals interactions, characterized as weak interactions. In this study, the computational tools Multiwfn and VMD (Visual Molecular Dynamics) were employed to investigate the strength of interactions within the molecular system. These tools facilitate the visualization and analysis of electronic properties, thereby enhancing our understanding of the underlying intermolecular forces. By integrating RDG and (λ2)ρ analyses, we aim to provide a more comprehensive perspective on molecular interactions and their significance in various chemical contexts.

Figure 3 reveals that the XY and EG-XY-EG monomers display regions of blue coloration surrounding hydrogen atoms, indicative of strong attractive interactions, such as hydrogen bonding or electrostatic interactions in these regions. The presence of green coloration in certain areas of all these monomers suggests the existence of weak van der Waals interactions, such as H-π interactions. Consequently, both hydrogen bonding and H-π interactions play significant roles in the interactions between drugs and drug carriers. Furthermore, the images suggest a predominance of strong interactions and a relative scarcity of repulsive interactions within these monomers.

4. Conclusion

This theoretical study using DFT calculations demonstrates that incorporating ethylene glycol (EG) into PLGA monomers significantly decreases their energy gap, with monomers such as XYXX-EG-XYXX and XXYYY showing strong potential as drug carriers. Increasing the ratio of lactic acid (X) to glycolic acid (Y) generally enhances the dipole moment of PLGA polymers, especially when the X to Y ratio is 3:1. Positioning EG between identical PLGA units (e.g., XY-EG-XY) markedly increases the dipole moment, highlighting the importance of monomer arrangement. Additionally, noncovalent interaction analysis indicates that selected PLGA monomers exhibit strong attractive and weak van der Waals interactions, which are beneficial for effective drug binding and controlled release, suggesting these monomers can form stable complexes with drug molecules.

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References:

[1] Haleem, A., Javaid, M., Singh, R.P., Rab, S., Suman, R. Applications of nanotechnology in medical field: a brief review. *Global Health Journal*. **2023**, 7, 70-7.

[2] Moshed, A.M.A., Sarkar, M.K.I., Khaleque, M.A. The application of nanotechnology in medical sciences: new horizon of treatment. *Am. J. Biomed. Sci*. **2017**, 9, 1-14.

[3] Fakruddin, M., Hossain, Z., Afroz, H. Prospects and applications of nanobiotechnology: a medical perspective. *Journal of nanobiotechnology*. **2012**, 10, 1-8.

[4] Klymchenko, A.S ,.Liu, F., Collot, M., Anton, N. Dye-loaded nanoemulsions: biomimetic fluorescent nanocarriers for bioimaging and nanomedicine. *Advanced healthcare materials*. **2021**, 10, 2001289.

[5] Surendiran, A., Sandhiya, S., Pradhan, S., Adithan, C. Novel applications of nanotechnology in medicine. *Indian Journal of Medical Research*. **2009**, 130, 689-701.

[6] Xu, Y., Zhang, L., Chen, G., Chen, P. Thinking on the application of nanotechnology in the mechanism research on the traditional Chinese medicine diagnosis and treatment of diabetes mellitus. In: Journal of Physics: Conference Series, IOP Publishing, **2011**, Vol. 276, p. 012050.

[7] Adekoya, O.C., Adekoya, G.J., Sadiku, E.R., Hamam, Y., Ray, S.S. Application of DFT calculations in designing polymer-based drug delivery systems: An overview. *Pharmaceutics*. **2022**, 14, 1972.

[8] Bouissou, C., Rouse, J., Price, R., Van der Walle, C. The influence of surfactant on PLGA microsphere glass transition and water sorption: remodeling the surface morphology to attenuate the burst release. *Pharmaceutical research*. **2006**, 23, 1295-305.

[9] Jain, R.A. The manufacturing techniques of various drug loaded biodegradable poly (lactide-co-glycolide)(PLGA) devices. *Biomaterials*. **2000**, 21, 2475-90.

[10] Quinten Ruhe, P., Hedberg, E.L., Torio Padron, N., Spauwen, P.H., Jansen, J.A., Mikos, A.G. Rhbmp-2 release from injectable poly (DL-lactic-co-glycolic acid). *Journal of bone and joint surgery. American volume*. **2003**, 85, 75-81.

[11] Allison, S.D. Effect of structural relaxation on the preparation and drug release behavior of poly (lactic-co-glycolic) acid microparticle drug delivery systems. *Journal of pharmaceutical sciences*. **2008**, 97, 2022-35.

[12] Mundargi, R.C., Babu, V.R., Rangaswamy, V., Patel, P., Aminabhavi, T.M. Nano/micro technologies for delivering macromolecular therapeutics using poly (D, L-lactide-co-glycolide) and its derivatives. *Journal of Controlled Release*. **2008**, 125, 193-209.

[13] Mohamed, F., Van Der Walle, C.F. Engineering biodegradable polyester particles with specific drug targeting and drug release properties. *Journal of pharmaceutical sciences*. **2008**, 97, 71-87.

[14] Gilding, D., Reed, A. Biodegradable polymers for use in surgery—polyglycolic/poly (actic acid) homo-and copolymers: 1. *Polymer*. **1979**, 20, 1459-64.

[15] Jeong, B., Bae, Y.H., Kim, S.W. Thermoreversible gelation of PEG–PLGA– PEG triblock copolymer aqueous solutions. *Macromolecules*. **1999**, 32, 7064-9.

[16] Becke, A.D. Density-functional thermochemistry. IV. A new dynamical correlation functional and implications for exact-exchange mixing. *The Journal of chemical physics*. **1996**, 104, 1040-6.

[17] Becke, A.D. Density-functional exchange-energy approximation with correct asymptotic behavior. *Physical review A*. **1988**, 38, 3098.

[18] Lee, C., Yang, W., Parr, R.G. Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. *Physical review B*. **1988**, 37, 785.

[19] Gaussian09, R., Frisch, M., GW, T., Schlegel, H., Ge Scuseria, M.R., Cheeseman, J., et al. Wallingford CT: Gaussian .*Inc*. **2009**, 121, 150-66.

[20] Lu, T., Chen, F. Multiwfn: A multifunctional wavefunction analyzer. *Journal of computational chemistry*. **2012**, 33, 580-92.

[21] William, H. VMD-visual molecular dynamics. *Journal of molecular graphics*. **1996**, 14, 33-8.

[22] Humphrey, W., Dalke, A., Schulten, K. VMD: visual molecular dynamics. *Journal of molecular graphics*. **1996**, 14, 33-8.

[23] Williams, T., Kelley, C., Bröker, H., Campbell, J., Cunningham, R., Denholm, D., et al. Gnuplot 4.5: an interactive plotting program. 2, *gnuplot. info*. **2017**, 56.

[24] Krauss, M., Stevens, W.J. Effective potentials in molecular quantum chemistry. *Annual Review of Physical Chemistry*. **1984**, 35, 357-85.

[25] McBride, B.J., Gordon, S. Computer program for calculation of complex chemical equilibrium compositions. **1972**.

[26] Chamorro, E., Chattaraj, P.K., Fuentealba, P. Variation of the electrophilicity index along the reaction path. *The Journal of Physical Chemistry A*. **2003**, 107, 7068-72.

[27] Fawcett, W.R. Thermodynamic parameters for the solvation of monatomic ions in water. *The Journal of Physical Chemistry B*. **1999**, 103, 11181-5.

[28] Jameson, C.J., Gutowsky, H. Calculation of chemical shifts. I. General formulation and the Z dependence. *The Journal of Chemical Physics*. **1964,** 40, 1714-24.

[29] Safi, Z., Wazzan, N. Investigation on the stability of the Enol Tautomer of Favipiravir and its derivatives by DFT, QTAIM, NBO, NLO and 1H-NMR. *Journal of Taibah University for Science*. **2023**, 17, 2269663.