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DOI
10.1007/s12247-024-09880-4

Publication date
2024

Document Version
Final published version

Published in
Journal of Pharmaceutical Innovation

Citation (APA)
Acharya, S., Aswath, S., Divi, S., Guru, B. R., Dey, P., & Vatti, A. K. (2024). Modelling of Prednisolone Drug Encapsulation in Poly Lactic-co-Glycolic Acid Polymer Carrier Using Molecular Dynamics Simulations. *Journal of Pharmaceutical Innovation*, *19*(6), Article 70. https://doi.org/10.1007/s12247-024-09880-4

Journal of Pharmaceutical Innovation (2024) 19:70
https://doi.org/10.1007/s12247-024-09880-4

ORIGINAL ARTICLE

Modelling of Prednisolone Drug Encapsulation in Poly Lactic-co-Glycolic Acid Polymer Carrier Using Molecular Dynamics Simulations

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Accepted: 16 October 2024

Abstract

Purpose Prednisolone, a synthetic corticosteroid drug, is extensively utilized to treat inflammatory diseases and regulates metabolism and the immune system in cancer treatment. However, these drugs are toxic and cause severe side effects if administrated for long durations and in large doses. This work intends to study the atomistic interactions of popular polymeric carrier like PLGA with the drug and thereby provide insights into achieving better loading and a sustained release.

Methods Molecular dynamics (MD) simulations of prednisolone (drug) encapsulated in Poly Lactic-co-Glycolic acid (PLGA) are performed in this study. Grand Canonical Monte Carlo (GCMC) simulations with MD simulations are conducted to determine the water penetration in PLGA polymer and polymer stability in water. The investigations from this study encompasses structural and dynamical parameters, including the end-to-end distance, radius of gyration of polymer chains, interaction energy, and diffusion coefficient of the drug.

Results The polymer-drug interactions are studied and identified from the simulation data of PLGA(75:25) and PLGA(50:50) polymers with prednisolone in an aqueous medium for optimal drug carrying capacity and effective drug release. Also, the polymeric systems of PLGA(75:25) and PLGA(50:50) are analyzed with the water penetrant loading using the Grand Canonical Monte Carlo (GCMC) and MD simulations. Water loading analysis revealed that PLGA(75:25) has the highest swelling compared to PLGA(50:50).

Conclusion This study highlights the characteristics and critical parameters for developing an optimal drug delivery system by investigating polymer-drug interactions, drug encapsulation, and water uptake in polymers using MD and GCMC simulations.

Keywords Prednisolone · Anti-inflammatory drug · Molecular dynamics simulations · PLGA · Encapsulation

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Introduction

Synthetic glucocorticoids (GCs) (most common ones being Prednisolone and Dexamethasone) are versions of steroid hormones which are released in our body when it is stimulated with stress [1]. These lipophilic drugs are widely accepted for the treatment of several inflammatory and autoimmune related diseases like chronic leukemia, asthma, central nervous system (CNS) lymphoma, arthritis, and help in nausea/vomit control, reduction of tumor associated edema [2–4]. GCs are one of the oldest and the most popular class of synthetic drugs used in modern medicines. They can be administered topically, intravenously, or even orally [5]. However, these GCs are immunosuppressants. They have proven to be neurotoxic and cause neuronal cell

Published online: 28 October 2024

loss with aging [6]. They cause several side effects like insomnia, depression, memory loss and mood swings when administered in large doses or used for a long period of time [7]. Even though prednisolone shows relatively lower activity and efficacy, it is known to exhibit lesser adverse effects as compared to dexamethasone [4]. Hence, it is of utmost significance to assess the potential advantages in relation to the risks involved [5, 8]. To resolve the drawbacks, there is a need to employ a favorable drug carrier that is not only bio-compatible, bio-degradable but also has better drug carrying capacity and provides a sustained release. Polymer-drug conjugates, polymeric micelles, polymeric nanoparticles etc. are some of the popular drug delivery vehicles [1, 9]. Polymer based drug delivery vehicles bring unique benefits that include superior drug pay load flexibility (hydrophobic/hydrophilic), easy surface modification and sustained release [10]. The primary objective of developing drug delivery systems is twofold: to create carriers with favorable pharmacodynamic properties and to ensure their bio-compatibility, while also enabling controlled release of the drug at specific target sites [11–14]. Significant developments have been made in this field over the past few decades for applications like tissue engineering, prosthetics, modifying bones, implants etc. [15, 16]. Several studies have also been conducted employing liposomic and polymeric nanoparticle drug carriers, with the latter showing results in favor of targeted and controlled drug delivery [17, 18].

Bio-polymeric nanoparticles (NPs) provide a wide range of applications due to their inherent characteristics such as biodegradability, bio-compatibility, and favorable mechanical properties. They also assist in achieving sustained release of the drug along with possible targeting abilities making them excellent drug carriers [19, 20]. Choice of the polymer-drug combination is a key step, as several desirable properties can be achieved, for e.g., lower chemical potential, molecular mobility, activation energy etc. [9, 21]. More attention has been given to polymers like Poly lactic-co-glycolic acid (PLGA) because in comparison to their conventional counterparts, they possess several properties in favor of effective drug delivery of therapeutics like peptides, proteins, vaccine, antigens, genes etc. [22, 23]. PLGA is a biodegradable polymer [22, 24, 25] formed by combining two co-polymers of lactic acid (LA) and glycolic acid (GA). LA is a hard hydrophobic polymer that degrades slowly and GA undergoes faster degradation due to its hygroscopic nature [7]. The solubility of the PLGA polymer is contingent upon the relative compositions of LA and GA. Several investigations show that as the GA:LA ratio is increased, the hydrophilicity also increases leading to faster degradation. Further studies concluded that the degradation constant of GA was 1.3 times higher than that of LA [23, 26, 27]. Food and Drug Administration (FDA) has granted approval for the use of PLGA in drug delivery applications, as it may be readily integrated into diverse systems [20]. Other major advantages of using PLGA are that it can be employed to encapsulate different kinds of drugs (hydrophobic or hydrophilic) due to its dual nature. It can also protect the drug from quick release and stealthiness could be incorporated into the NPs by modifying the surface properties (PEGylation) [28–30]. Proteins, genes, antigens and other macromolecular drugs have been encapsulated in PLGA or PLGA based nanoparticles, and tested for drug delivery [31]. Hence, understanding the interactions between PLGA and drug will help us in rationale design to release the drug in safer quantity, thereby reducing the side effects [2].

In a prior study [2], prednisolone was encapsulated in PLGA(50:50) and its effectiveness was investigated on C6 cell lines. The drug release seen in the *in vitro* study exhibited a biphasic pattern, characterized by an initial rapid release of the drug, followed by a gradual and sustained release over time. Free prednisolone drug exhibits a short half-life. Nevertheless, when the drug is enclosed within PLGA NPs, it can be protected from the external surroundings for an extended duration. Overall, the Prednisolone containing NPs could control the cytokine release and inhibit the cell growth for a longer period as compared to the free drug. A previous work also studied the effect of prednisolone loaded PLGA NPs that were functionalised with folic acid (FA) moiety on C6 and U87 glioma cell lines [32]. It was concluded that the prednisolone could inhibit the cell growth better and had a sustained effect, when the FA moiety was present on the surface of the NPs than in its absence.

Pharmacological drug delivery systems could also be analysed at a molecular level by employing molecular dynamics (MD) simulations, which simulate the movement of atoms and molecules in a system over time [33–35]. The structure, dynamics, and interactions of drug molecules with polymeric delivery vehicles can be elucidated by MD simulations [36–38]. Moreover, these simulations can enable the optimization of drug delivery strategies. The simulations can predict the characteristics and different intermolecular interactions, such as electrostatic and van der Waals interactions, among drug-polymer systems, solubility parameter, mobility of drug in a polymer matrix [37] and the encapsulation efficiency [39].

Andrews et al. [40] studied the atomic-level mechanical properties of PLGA. They conducted molecular dynamics simulations of five samples of PLGA(50:50) based on the polymer's molecular weight in condensed phases. The samples had molecular weights ranging from 1579 u to 20183 u. The sample with reduced molecular weight exhibits more favorable properties in terms of energetics compared to the other four samples. Stipa et al. [41] investigated the drug-loaded nanoparticles made of poly(lactic acid) (PLA) and PLGA using molecular dynamics simulations and evaluated the model drugs such as Paracetamol, Prednisolone, and Isoniazid. They considered PLA polymer system with 112 units of lactic acid, whereas PLGA comprised of 81

units of lactic acid and 27 units of glycolic acid. The systems being assessed were simulated with and without the model drugs, resulting in a total of eight distinct systems: free PLA, PLA-Paracetamol, PLA-Prednisolone, PLA-Isoniazid, free PLGA, PLGA-Paracetamol, PLGA-Prednisolone, and PLGA-Isoniazid. Prednisolone was found to strongly interact with lipophilic parts of polymers in MD simulations, resulting in the maximum amount of drug being encapsulated. The binding energy affinities of Prednisolone for both polymer systems confirmed this.

The previous experimental works on prednisolone-PLGA NPs highlight many aspects related to drug loading, size and release. However, it is important to obtain molecular insights into prednisolone-PLGA NPs on varying the composition ratios of the lactic acid and glycolic acid for better encapsulation using the MD simulations. Our comprehension of drug interactions with biodegradable polymers can be improved by MD based study. The atomistic perspective provides us with valuable insights which can guide the drug kinetic experiments. Furthermore, conducting experimental research on a broad spectrum of the customized co-polymers is often challenging, expensive, as well as time-consuming. Computational based design of an effective drug carrier utilizing MD simulations can significantly assist in optimization of the size, shape, surface chemistry, drug concentration in polymer carriers, and drug localization within the polymer matrix in aqueous solution [39, 42]. In this work, we have probed PLGA(50:50) and PLGA(75:25) polymers loaded with prednisolone at different drug concentrations, and critically analyzed their interaction energies using MD simulations. Other important parameters like diffusivity of prednisolone, end-to-end distance and radius of gyrations of the PLGA polymer chains, hydrogen bonds have been probed at different drug concentrations. Additionally, we utilized Grand Canonical Ensemble Monte Carlo (GCMC) and MD simulations to probe the water uptake and swelling behavior of the PLGA(50:50) and PLGA(75:25) polymers.

Computational Details

Desmond [43] Molecular Dynamics package within Schrödinger [44] material science suite is used to carry out the MD simulations. We have used latest Optimized Parameters for Liquid Simulations (OPLS4) [45] force fields. The TIP3P water model is used to describe water. The glucocorticoid used was prednisolone (Pred) ($C_{21}H_{28}O_5$) as shown in Fig. 1 (left) and the polymers combinations used are PLGA(75:25) and PLGA(50:50). PLGA(75:25) comprised of 75% composition of Lactic Acid (LA) and 25% of Glycolic Acid (GA), while the PLGA(50:50) had 50% of both LA and GA as shown in Fig. 1 (right). Each PLGA contains 100 monomer units for e.g. PLGA(50:50) contains 50 monomers of LA and 50 monomers of GA. PLGA(75:25) molecular weight is 6873.751 g/mol and PLGA(50:50) molecular weight is 6523.074 g/mol. Details about number of molecules and box size dimensions are presented in Table 1. The MD simulations are performed for both 30% and 50% drug concentrations. Martyna-Tobias-Klein barostat with isotropic coupling having a relaxation time of 2 ps and Nose-Hoover thermostat with a relaxation time of 1 ps are used. Each system was subjected to MD simulations of NPT for 20 ns to achieve the equilibration volume. Later, equilibrated volume is used to perform MD simulations of NVT ensemble for 80 ns respectively, with a time step of 2 fs and a temperature of 310 K [37, 46, 47]. The pressure of 1 atm is used for the NPT ensemble to obtain the equilibrium density. The drug concentrations considered are calculated using Eq. 1.

We have employed drug-polymer mass ratio for quantification as it focuses on active components, i.e., drug and polymer that have a direct impact on the nanoparticles' therapeutic efficacy and release profiles. Solvents, surfactants, binders, and other components that are not necessary for the drug's therapeutic activity get included in the total mass. Higher drug concentrations can affect the physical properties of the nanoparticles, such as size, stability, and release kinetics. By focusing on the drug-to-polymer ratio, we can deepen

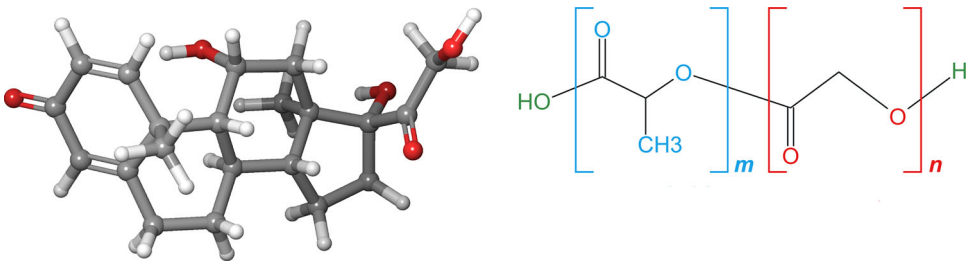

Fig. 1 (left) 3D structure of prednisolone. White spheres indicate hydrogen atoms, red indicate oxygen atoms and grey spheres indicate carbon atoms.(right) 2D sketch of the PLGA polymer. 'm' represents number of lactide units and 'n' represents number of glycolic units

Table 1 The number of prednisolone, polymer chains, water molecules and box dimensions used in the respective system

Drug concentration (%)	Prednisolone molecules	Number of polymer chains	Number of water molecules	Simulation box size ($Å^3$)
PLGA(50:50)				
30%	27	5	80846	137.781×137.847×136.928
50%	91	10	64016	126.601×129.825×126.601
PLGA(75:25)				
30%	29	5	56380	123.644×121.596×121.958
50%	96	10	95037	145.667×148.227×144.948

our understanding and optimize these properties for effective drug delivery [48–50]. Figure 2 shows the simulation box of the atomistic structure entailing the prednisolone-PLGA system in an aqueous solution for 30% drug concentration and PLGA(75:25) composition.

$$Drug\ Concentration = \frac{drug\ mass}{polymer\ mass} \times 100 \quad (1)$$

Results and Discussion

Interaction Energy

Pred- water (Drug-water), PLGA- water (Polymer-water) and Pred-PLGA (Drug- Polymer) pairs interaction energies are calculated. The electrostatic and the van der Waals (VdW) interaction energies are obtained. Total energy is the sum of the van der Waals and electrostatic energies. Table 2 summarizes the interaction energy values obtained for selected pairs. All the energy values are obtained to be negative which implies that all the interactions are dominantly attractive. For 30% drug concentration, Pred-polymer (PLGA(50:50)) van der Waals energy is the most attractive, i.e., -8.362 kcal/mol in comparison to the -6.725 kcal/mol for the PLGA(75:25). Overall, total energy is most attractive for the Pred-PLGA(50:50) at 30% drug concentration. Further, at 50 % drug concentration, Pred-PLGA(75:25) interaction is most dominant, i.e., -16.135 kcal/mol. Polymer-water interactions at various drug concentrations are found to be attractive. On observing all fours systems, it is clear that drug-polymer has the strongest attractive forces for PLGA(75:25) at 50% drug concentration and PLGA(50:50) at 30% drug concentration This can be attributed to the hydrophobic nature of LA, which allows dominant interaction between PLGA(75:25)-prednisolone, thus making the system stable.

End-to-End Distance

The investigation of the statistical measure of polymer chains necessitates the examination of a fundamental and critical quantity known as the end-to-end distance. This distance refers to the spatial separation between the two ends of a polymer chain. The worm-like chain model [51], is employed in order to compute the end-to-end distance, taking consideration of the presence of semi-flexible side chains [52]. The end-to-end distance of the polymers, averaged over all polymer molecules in the system, over the whole 80 ns duration of the molecular dynamics (MD) simulation production run, is computed using Equation [52] as shown in Fig. 3(a) and (b).

$$\left\langle h^2 \right\rangle = 2L_P L_0 \left[1 - (L_P/L_0)\left(1 - \exp\left(-L_0/L_P\right)\right)\right] \quad (2)$$

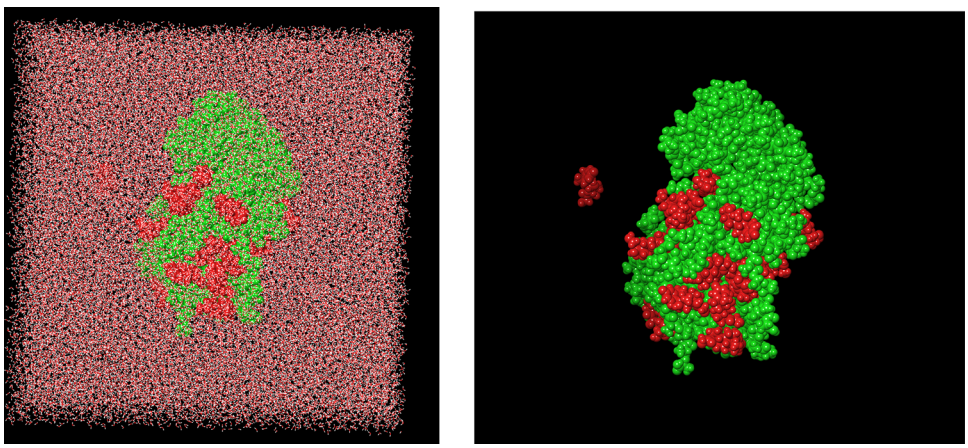

Fig. 2 A snapshot of prednisolone (Left) NVT trajectory snapshot for 30% drug concentration with explicit water molecules shown and (Right) NVT trajectory snapshot for 30% drug concentration without explicit water, water molecules hidden for clear view of drug-polymer. Polymer and drug are shown vdW sphere representation. The green color denotes PLGA (75:25) polymer and red denotes prednisolone

Table 2 The average interaction energies between prednisolone-polymer, prednisolone-water and, polymer-water are presented below

Interaction pair	Prednisolone-polymer		Prednisolone-water		Polymer-water	
	Electrostatic	van der Waals	Electrostatic	van der Waals	Electrostatic	van der Waals
30% drug concentration						
Interaction energy (kcal/mol) (PLGA (50:50))	−1.295	−8.362	−0.00287	−0.0000336	−0.00464	−0.00076
Total interaction energy (kcal/mol)	−9.657		−0.00291		−0.0054	
Interaction energy (kcal/mol) (PLGA (75:25))	−0.626	−6.725	−0.00186	−0.00057	−0.00824	−0.00451
Total interaction energy (kcal/mol)	−7.351		− 0.00243		−0.01275	
50% drug concentration						
Interaction energy (kcal/mol) (PLGA (50:50))	−3.459	−8.895	−0.00732	−0.00055	−0.01763	−0.00976
Total interaction energy (kcal/mol)	−12.354		−0.00788		−0.0274	
Interaction energy (kcal/mol) (PLGA (75:25))	−4.399	−11.7364	−0.01241	−0.00018	−0.00359	−0.00236
Total interaction energy (kcal/mol)	−16.135		−0.01259		−0.00595	

The units are in kcal/mol

where L_P is the persistence length, $\langle h^2 \rangle$ is the mean squared end-to-end distance, and L_0 is the extended chain length.

The values of the end-to-end distances, persistence lengths and extended chain lengths of all the systems can be seen in Table 3. It is observed that the end-to-end distances of the polymers increased as the drug concentration also increased. The persistence length is the bond length between monomers in the backbone for block co-polymers. In this study, the persistence length is found to increase with increase in drug concentration, thus more flexibility and better interactions. The shorter persistence length shows the folding nature of the PLGA polymer in aqueous environment. Within the same drug concentration, the PLGA(50:50) polymers were found to have higher persistence lengths at both 30% and 50% drug concentrations. The end-to-end distance was found to increase with increase in drug concentration for both PLGA(75:25) and PLGA(50:50). The end-to-end distance of PLGA (50:50) is around 32.19 Å in 30% drug concentration, where as 35.71 Å in 50% drug concentration. The extended lengths of 381 Å is observed for all the considered polymers in this work. The longer extended chain length suggest that, we have used the long polymer chain to encapsulate the prednisolone. Overall, PLGA(50:50) polymer is found to have a flexible structure for both 30% and 50% drug concentrations.

Radius of Gyration

Intuitively, the radius of gyration (ROG) enables the investigation of the rigidity of the polymer coil. In our work, we determine the ROG of PLGA (75:25) and PLGA (50:50). The following equation can be used to calculate the ROG (R_g).

$$R_g = \sqrt{\frac{1}{N}\sum_{i=1}^{N} \mid r(i) - r_{centre} \mid^2} \tag{3}$$

where N is the total number of monomers, $r(i)$ and r_{centre} are the coordinates of a monomer i and the centre of mass, respectively. R_g

Table 4 ROG and the standard deviation (σ) values (in Å) at two different drug concentrations for considered PLGA polymers

Polymer (LA:GA)	Radius of gyration (Å)	σ (Å)
30% drug concentration		
PLGA (50:50)	14.02	0.365
PLGA (75:25)	13.14	0.162
50% drug concentration		
PLGA (50:50)	16.20	0.167
PLGA (75:25)	14.46	0.137

The calculated R_g values for PLGA polymer chains of concentrations 30% and 50% are presented in Table 4. The calculated R_g as a function of time is shown in Fig. 3(c) and (d) at 30% and 50% drug concentration. Higher the ROG, better is the dispersion of the drug in the polymer, enabling a more stable and better encapsulation. The PLGA (50:50) have higher radii of gyration than PLGA (75:25) for both the drug concentrations, hence is more stable. It is also noticed that the ROG increased with increase in drug concentration. This is due to the fact that as ROG increases, the monomers move away from the centre of the mass. As a result, the number of drug molecules closer to the centre of mass increases, resulting in better drug entrapment.

Hydrogen Bonds

In the context of how drugs interact with polymers and with water, hydrogen bonding is essential. The enhanced interactions between the polymer and the water primarily support the polymer's hydrophilicity. In this study, the hydrogen bonds between two pairs—drug-polymer and polymer-solvent—are computed. The variation of the hydrogen bond for PLGA (50:50)-Prednisolone and PLGA (50:50)-water at 30% drug concentration is shown in Fig. 4(a) and (b).

Table 5 presents a summary of the average number of hydrogen bonds observed in the PLGA-water and PLGA-prednisolone systems at various concentrations of the drug.

Table 3 The end-to-end distance, persistence length, extended chain length (in Å) along with time series standard deviation (σ) with respect to end-to-end distance values are summarized for considered PLGA polymers at different drug concentrations

Polymer	End-to-end distance (Å)	Persistence length (Å)	Extended chain length (Å)	σ (Å)
30% drug concentration				
PLGA (50:50)	32.19	1.71	381.32	2.70
PLGA (75:25)	25.54	1.09	381.15	3.59
50% drug concentration				
PLGA (50:50)	35.71	2.05	380.67	1.36
PLGA (75:25)	30.39	1.39	381.05	1.65

The end-to-end distance was averaged over 80 ns of simulation time

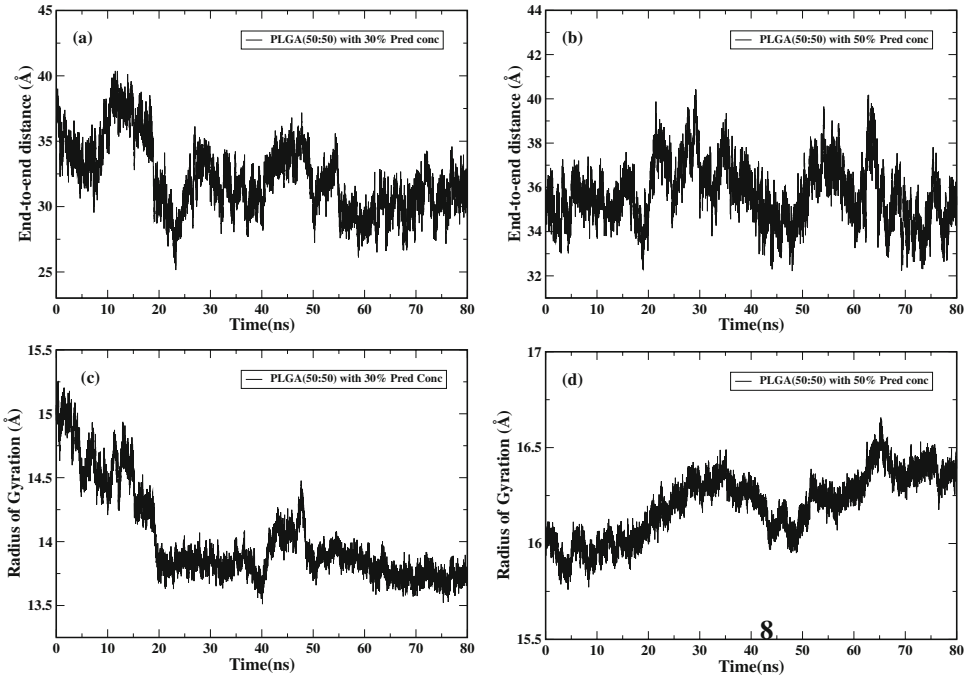

Fig. 3 End-to-end distance versus simulation time for (a) PLGA (50:50) for 30% drug concentration (b) PLGA (50:50) for 50% drug concentration. Radius of gyration versus simulation time for (c) PLGA (50:50) for 30% drug (d) PLGA (50:50) for 50% drug concentration

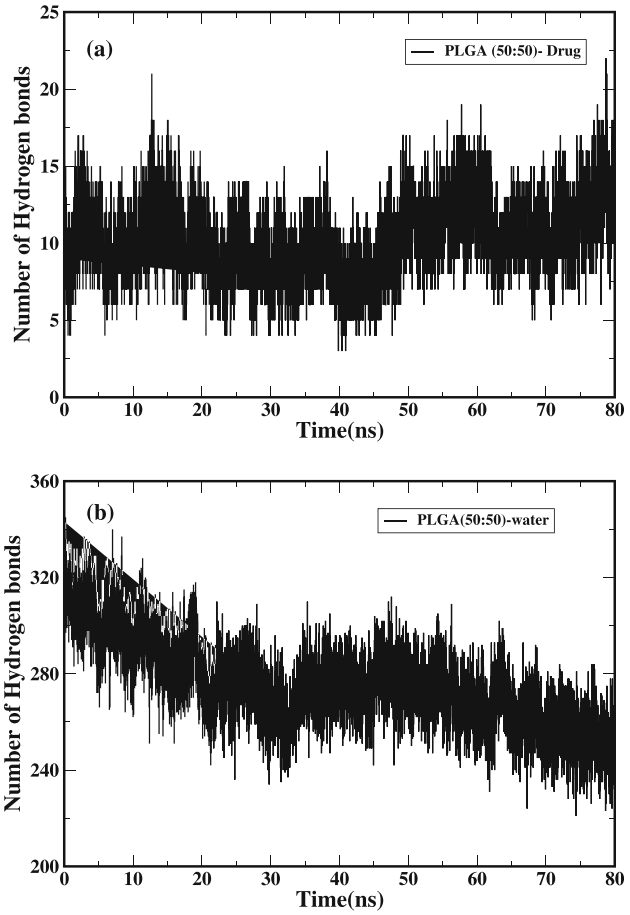

Fig. 4 The hydrogen bonds for (a) PLGA(50:50)-Drug (b) PLGA(50:50)-Water versus simulation time at 30% drug concentration

The hydrogen bonds play a vital role in providing us information about the interactions between the selected molecules. In this study, the number of hydrogen bonds are averaged for the systems and different drug concentrations. In 30% drug concentration, the number of H-bonds in the PLGA (50:50)-water system is slightly higher than the PLGA(75:25). However, PLGA-pred H-bonds increased for PLGA (75:25)-Pred than the PLGA(50:50) for this particular drug concentration. The exact opposite trend was observed for the 50% drug concentration for the selected pairs. On overall comparison, it was observed that with increase in drug concentration, the number of H-bonds rose drastically. It is also interesting to note that there is increase in number of H-bonds between PLGA(50:50)-Pred at the 50 % drug concentration in comparison to the PLGA(75:25). Therefore, favoring PLGA(50:50) to load higher drug concentrations for the targeted delivery applications.

Diffusion Coefficient

The diffusivity averaged among all prednisolone drug molecules is computed using the Equation [53].

$$D = \frac{1}{6}\lim_{t\to\infty}\frac{d}{dt}\left\langle \mid \vec{r}(t) - \vec{r}(0) \mid^2 \right\rangle \tag{4}$$

where $\left\langle \mid \vec{r}(t) - \vec{r}(0) \mid^2 \right\rangle$ is the mean-square displacement. Table 6 consists of all the diffusion coefficient values obtained within this study. For the 30% drug concentration, the diffusion coefficient increased by almost 2.5 times for the PLGA (50:50) in comparison to PLGA (75:25). The

Table 5 The average number of hydrogen bonds for selected PLGA-water, PLGA-prednisolone and ratio of PLGA-prednisolone to PLGA-Water at varying drug concentrations

Polymer	Polymer-Water	Polymer-prednisolone	Ratio of polymer-prednisolone to polymer-water
	Average number of H-bonds		
30% drug concentration			
PLGA (50:50)	276	10	3.62 %
PLGA (75:25)	269	16	5.94 %
50% drug concentration			
PLGA (50:50)	479	40	8.35 %
PLGA (75:25)	548	31	5.65 %

prednisolone mobility is higher in PLGA (50:50) at 30 % drug concentration than the 50 % drug concentration, i.e., 5.98×10^{-10} m^2/s and 1.36×10^{-10} m^2/s. Further, the mobility of prednisolone is higher in PLGA (75:25) in 30 % drug concentration than the 50 % drug concentration, i.e., 2.26×10^{-10} m^2/s and 1.49×10^{-10} m^2/s. Based on the PLGA (50:50) and PLGA (75:25) mobility trends, it can be interpreted that faster release of prednisolone can be achieved using PLGA(50:50).

Water-Uptake Using Grand Canonical Monte Carlo and Molecular Dynamics Simulations

We conducted penetrant loading simulations to simulate the water uptake in PLGA(50:50) and PLGA(75:25). These calculations run through two different simulation stages several times, as determined by the total simulation time. In the initial phase, a Grand Canonical Monte Carlo (GCMC) simulation is conducted. This simulation involves the addition or removal of water molecules in a manner that strictly aligns with the applied chemical potential (μ). The purpose of this simulation is to sample states from the grand canonical (μVT) ensemble. A comprehensive derivation of the statistical mechanical foundation of GCMC algorithms can be seen in Frenkel & Smit [53]. The second stage involves conducting an NPT MD simulation to effectively explore and analyze molecular rearrangements and conformations throughout the entire system. During each iteration, a 4.8 picoseconds MD simulation is conducted, which is then followed by 5000 GCMC steps. We conducted simulations at a relative humidity of 100 % which is directly correlated with the chemical potential. The simulations were conducted over a duration of 100 nanoseconds using an NPT ensemble at a temperature of 310 K and a pressure of 1 atm.

Water penetration leads to sequence of significant events such as the expansion and subsequent degradation of the PLGA polymer [54, 55]. The regions with a higher proportion of lactide, which are more hydrophobic than the glycolide regions, have a tendency to spontaneously entangle with one other and reduce their interaction with water. Figure 5(a) illustrates the time variation of water weight percentage (wt %) for two distinct polymers, namely PLGA(75:25) and PLGA(50:50). The water penetration is found to be greater in PLGA(50:50), i.e., at 8.92 wt %, compared to PLGA(75:25), i.e., 5.73 wt %. This may be explained by the improved interaction between the polymer's glycolic acid component and water, which is substantially higher in PLGA(50:50) than in PLGA(75:25).

Conclusions

In this work, prednisolone encapsulation in PLGA was comprehensively investigated by employing MD simulations. Two different PLGA polymers namely PLGA(50:50) and PLGA(75:25) were mainly investigated to understand the

Table 6 The calculated diffusion coefficients (in m^2/s) are shown for Prednisolone in PLGA for the considered drug concentrations

Drug concentration	Prednisolone diffusion coefficient (m^2/s)	σ (m^2/s)
PLGA(50:50)		
30 %	5.98×10^{-10}	4.18×10^{-13}
50 %	1.36×10^{-10}	6.25×10^{-14}
PLGA(75:25)		
30 %	2.26×10^{-10}	3.71×10^{-13}
50 %	1.49×10^{-10}	1.30×10^{-13}

The time series standard deviation (σ) is also presented

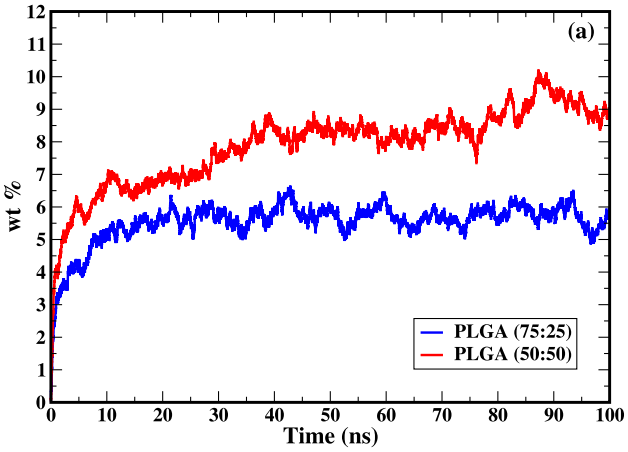

Fig. 5 (a) Weight percent of the penetrant versus total simulation time for both the polymers, PLGA(50:50) and PLGA(75:25)

carrying capacity of prednisolone drug. MD simulations reveal the interaction energy for all the selected pairs were attractive, especially for the case of PLGA- prednisolone. Radius of gyration results showed that PLGA(50:50) is rigid in comparison to the PLGA(75:25). The hydrophobic effect in the encapsulation of Prednisolone with PLGA(50:50) is less pronounced compared to that with PLGA(75:25). This is because drug molecules tend to align closely with the PLA units of the PLGA(75:25) structure, enhancing hydrophobic interactions due to high number of LA units. The end-to-end distance calculations concluded that, overall, PLGA(50:50) is more flexible in both the drug concentrations. Based on the in-depth H-bond analysis, PLGA(50:50)-Pred at the 50 % drug concentration was found to be most favorable in comparison to the PLGA(75:25). Furthermore, our GCMC simulations conclude higher amount of water loading for PLGA(50:50) than PLGA(75:25) due to the enhanced interaction of glycolide part in PLGA(50:50) polymer. On many accounts it is observed that PLGA(50:50) can be potentially used to load higher prednisolone drug concentrations for the targeted delivery applications. In conclusion, as demonstrated in this work, state of the art MD simulations can play a vital role in selection of polymers for drug encapsulation. The underlying approach is applicable to any other hydrophobic drug as well. The final conclusion is that the PLGA(50:50) could be selected for higher mobility of prednisolone drug based on the MD simulations.

Acknowledgements Anoop Kishore Vatti would like to thank Shrödinger Centre for Molecular Simulations, Manipal Academy of Higher Education (MAHE), Manipal for their support.

Funding Not applicable.

Data Availability Not applicable.

Declarations

Conflicts of Interest The authors declare no conflict of interests.

Ethical Declaration No human subjects or animals were used during this research work.

Ethics Approval Not applicable.

Consent for Publication Not applicable.

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