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Molecular simulation of gabapentin intercalation in the interlayer space of Zn_2 AL-LDH: Molecular dynamic of drug delivery

Jila Talat Mehrabad [1, *], Farzad Arjomandi Rad [1, *], Mehrdad Molaei[1]

[1] *Department of Chemistry, Bonab Branch, Islamic Azad University, Bonab, Iran*

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ABSTRACT

Drug delivery is the process of administering drugs or other drug compounds to achieve a therapeutic effect. Drug delivery has become an important issue in the pharmaceutical industry in the last few decades, with the use of this system, the speed of drug release as well as drug control by doctors is possible. Layered double hydroxides (LDHs) are a group of anionic clays with a structure It is a layer with good drug release control properties. In this work, the molecular simulation (quantum) and (molecular dynamics) of the drug gabapentin interlayered in Zn_2Al-LDH were carried out. First, the modeled gabapentin molecule was quantum simulated by the DFT method. Properties extracted from quantum studies such as partial molecular charge and molecular orbitals were investigated, and then after designing a special cell for the Gabapentin-Zn_2Al-LDH combination, classical mechanics and molecular dynamics simulation were performed. Finally, important properties such as X-Ray diffraction comparison were calculated. experimentally (in past work). The characterization results of the Zn_2Al-LDH nanohybrid also showed that there is a good agreement between the X-ray diffraction and the simulated XRD (d_{003}=8.74 Å) and the angular distribution of the drug was relatively horizontal. According to molecular dynamic simulation, the results of Mean Square Displacements or MSD (the simulated drug delivery) showed that water molecules were released faster than drug molecules from the Zn_2Al-LDH hybrid structure (0.11 intensity of water per time step versus 0.07 of drug).

1. Introduction

Drug delivery is the process of administering drugs or other drug compounds to achieve a therapeutic effect. Drug delivery has become an important topic in the pharmaceutical industry in recent decades, as scientists have concluded that the effectiveness of a drug can be influenced by the method by which the drug is delivered to the body [1]. Drug release systems in recent years, in particular, there have been tremendous advances in drug delivery technology. For example, advanced drug delivery systems, such as transdermal patches, can deliver a drug more selectively to a specific site, often resulting in a lower dose and an easier and more precise delivery [2]. Computational studies on the adsorption of various molecules, including gases, environmental pollutants, and drugs, have attracted the attention of researchers, providing valuable insights into molecular interactions and the design of efficient delivery systems [3-5]. Layered double hydroxides (LDHs) are a group of anionic clays with a layered structure [6] whose cations are formed by two metals aluminum (Al^{3+}) and zinc (Zn^{2+}) [7]. The composition of two-dimensional layered materials and the interlayer technique have created a new era in the development of nanohybrids [8]. The layer of double

∗ Corresponding authors; e-mail: fdanesh23@gmail.com & jila.talat@gmail.com
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hydroxides (LDH) is a mineral material made with a positive charge and consists of layers of the type (brucite) of mineral materials including hydrated magnesium hydroxide in white, gray, and green colors and a mixture of metal hydroxides [9]. Because most biomolecules have a negative charge, they can be placed in LDH spaces. A variety of drugs can also be transported with LDH for controlled release [10]. Layered Double Hydroxides (LDHs) have gained increasing attention in the field of drug delivery due to their unique properties [11]. LDHs have a high loading capacity and controlled release characteristics, making them ideal candidates for efficient drug delivery systems. LDHs are known for their biocompatibility and ability to protect drugs from degradation in the body [12]. This targeted approach can improve drug efficacy while minimizing systemic side effects of the drug. Overall, LDHs offer a promising potential for personalized and targeted drug delivery strategies, leading to improved patient outcomes and enhanced treatment efficacy [13]. By combining the unique properties of LDHs with advanced drug delivery techniques, researchers can develop highly efficient and targeted drug delivery systems [14]. These systems can improve the bioavailability of drugs and enhance their therapeutic effects by delivering drugs directly to the target site [15]. LDHs can also protect drugs from degradation in the gastrointestinal tract, ensuring their stability and effectiveness upon reaching the intended site of action [16]. In addition, LDHs can encapsulate both hydrophilic and hydrophobic drugs, making them suitable carriers for a wide range of pharmaceutical compounds. LDHs can be designed with controlled release properties for sustained drug delivery over a prolonged period [17]. Gabapentin is an anticonvulsant drug used to treat paroxysmal seizures, neuropathic pain, hot flashes, and restless legs syndrome. This drug is recommended as one of the first-line drugs for the treatment of neuropathic pain caused by diabetic neuropathy, post-shingles neuralgia, and central neuropathic pain. Gabapentin causes neuroplastic changes in the sensitized nervous system. The effect of the above drug is probably caused by a decrease in neuronal sensitivity caused by inflammation or nerve damage [18]. Computational methods such as quantum study and molecular dynamic simulation are carried out to investigate the properties of the interaction of drugs with nanometers as a novel drug delivery system [19,20]. Recently Ghiasi et al. have investigated computational studies on the structures and properties of drugs [21-27].

Molecular dynamic simulation of drug interlayer and drug transport and release by LDHs is critical because it must be determined at what time, place, and under the influence of what effective factors the drug is released [28]. In 2011, Pospishel et al. conducted a molecular simulation study of LDH mixed with porphyrin. In this research, molecular calculations were used to analyze the structure of different layered structures of double-layer hydroxides (LDH) with different porphyrin anions. The simulations were performed in Cerius2 and *Materials Studio* modeling environments. The calculated structures were carefully extracted based on the experimental results and the presented models agree with them [29]. In 2020, Pesinka et al. studied the structural arrangement and properties of bilayer hydroxide nanocarriers dissolved with sulindac and mefenamic acid by molecular simulation methods, which molecular simulation methods are used to solve the crystal structures and interlayer arrangements of bilayer hydroxides dissolved with sulindac and mefenamic acid [30]. In 2018, Sanchez et al. evaluated a molecular dynamics framework to explore the structure and dynamics of double-layered hydroxides. In this study, a simple method based on the CLAYFF force field to perform molecular dynamics (MD) is presented. It has the potential to model various important applications of LDH, including ion exchange and interlayer equilibrium processes in various areas such as drug delivery, water treatment, and corrosion protection. A magnesium-aluminum-based LDH with a metal ratio of 2:1 (Mg_2Al) was selected for computer validation [31]. "Molecular Dynamics Framework" to investigate the structure and dynamics of bilayer hydroxides. An extract from their study was that LDH is more affected by the charge density of the anions than the size of the anions. This computational framework is considered promising for the analysis of the intercalation and anion exchange mechanisms in LDH. A model of LDH in solution can help understand the natural hydration/dehydration state of each LDH interlayer [32]. In biomedical applications, different types of LDH are being used for drug delivery. Although these are still in their infancy, the results are promising and may be useful for other delivery systems that have reached advanced levels of clinical trials and are becoming more widely used [33]. Interesting specific applications of nanoparticles in general, and LDH in particular, include alternative drug delivery systems, due to the in situ sustained release, high intrinsic pharmacological activity, high adsorption capacity, high solubility, and large surface area of the LDH drug system compared to other drug systems, and as medical carriers [7]. In particular, the simulation calculations of relatively large acidic drugs have not been performed on a large scale, so the appropriate configuration of these anion species in the space between the LDH layers according to the drug release properties of these nanohybrid

compounds is hardly justified. Meanwhile, the polar and acidic ends of the drug anions form non-bonded interactions and suitable long-range intermolecular forces with the hydroxide layers. Therefore, in this study, we attempted to study the molecular simulation of the interlayer of gabapentin drug in the interlayer space of Zn_2Al-LDH by quantum studies and the release of the drug in this space.

2. Computational Details

All modeling and simulations with *Dmol3* and *forcite* code in the software material Studio 2017 have been done [34]. These codes include valid energy fields for geometric optimization, structure energy minimization and output analytical properties for periodic solids, and force fields that can be used well in the study of molecular systems and crystalline materials. First of all, a hexagonal LDH supercell was designed during the research. We used the Dmol3 program at the GGA-PBE/DNP [35,36] level to optimize the gabapentin structure. to find a geometrically optimized configuration of gabapentin. Following the definition of atomic charges, this data was utilized in spatiotemporal dynamics simulations. The use of a classical drying force field was associated with this system [37, 38]. The first step in preparing the model of the displaceable species is the construction of positively charged host layers. $Zn_4Al_2(OH)_{12}CO_3.3H_2O$ hydroxide layers were made using hydrotalcite crystal structures that were previously reported in previous research [39]. As seen in Fig. 1, it hosts a three-layer structure that includes rhombohedral networks with a unit cell with the following parameters: a=b=3.06616A˚, α=β=90◦, γ=120◦, c=22.6164 A˚, whose space group is $R\bar{3}m$ (166). To study the relationship arrangement of guest species and the interlayer space, a P1 supercell with dimensions 3a x 2b x $3d_{exp}$ was made, which d_{exp} was obtained from the experimental XRD data for gabapentin-LDH. The interlayer carbonate ions and water molecules were first removed from the interlayer space. Then the supercell was developed with dimensions 3a × 2b × 1.150c with parameters 3a = 9.19848 Å, 2b = 6.13232 Å, and 1.150c = 26.22 Å. so that d_{exp}= 8.74 Å, the ratio of zinc atoms to aluminum atoms is 2. The zinc and aluminum atoms are distributed in any layers. Each hydroxide layer consists of four Zn^{2+} ions and two Al^{3+} ions, also trivalent dictations should not be arranged in adjacent octahedral units. The gabapentin molecule can be seen in planer form in Fig. 2 gabapentin anions with two numbers were placed in the interlayer area of LDH to neutralize the positive charge of the hybrid system and form a two-layered structure. The internal space between the layers contains randomly placed water molecules (three in total). The atomic charges are derived from Mulliken charges, APT [40] charges, and usually ESP charges. In this research, as shown in Table 1 the atomic charges of gabapentin molecules are determined by the ESP method from the optimized geometrical configuration of gabapentin through the DFT [41,42]. (Fig. 3)

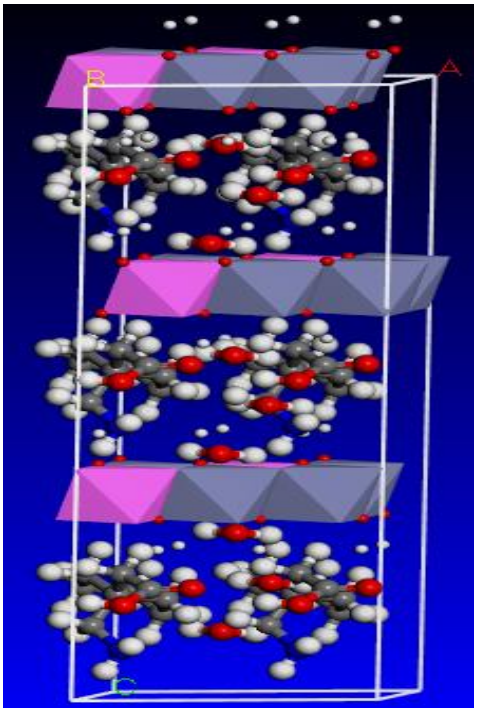

Fig. 1. The structure of the designed supercell of Gabapentin-Zn_2Al-LDH.

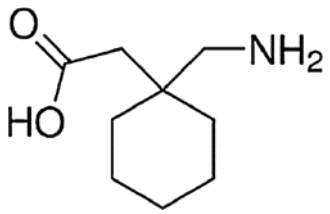

Fig. 2. Chemical structure of Gabapentin

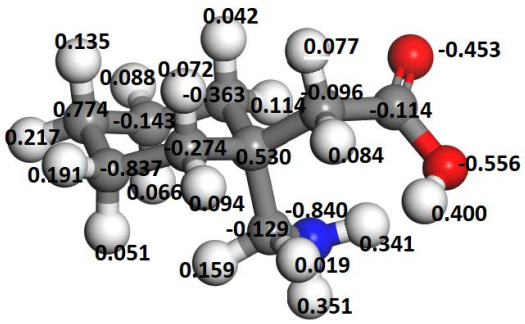

Fig. 3. Calculated partial atomic charges of Gabapentin-Zn_2Al-LDH by ESP method resulting from geometric optimization.

The charges of the layers are firstly calculated by the charge equilibration (QEq) method according to Fig. 4. Because the dreiding force field is suitable for Zn-Al-LDH [43]. The LDH partial charges were modified by the dreiding force field and the partial charges for different atoms were obtained. The charges of LDH layers were adjusted as follows considering the improved force field and partial charges.

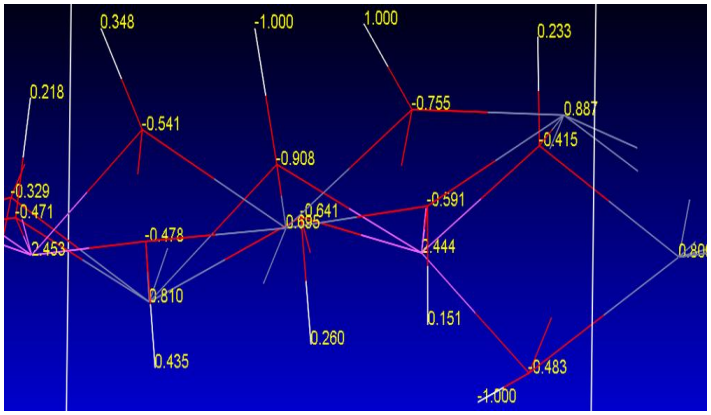

Fig. 4. Calculated partial charges for Zn_2Al-LDH layers by the charge equilibration (QEq) method.
Al: 2.453 or 2.444 Zn: 0.810 or 0.695 O: -0.755 or -0.415
H: 0.348 or 0.233

A driving force field was utilized in the initial configuration to fully optimization. The electrostatic energy was calculated using the *Ewald* summation method [44] and the van der Waals energy was expressed as a Lennard-Jones potential [45]. According to the conditions of all the atoms of host layers during the optimization time, they are considered hard units, and the parameters a, b, and c of the unit cell were variable, thus optimizing the arrangement of host layer atoms became possible. Also, all the atomic positions in the interlayer section were variable [46].

Table 1. ESP-fitted charges of gabapentin.

n	Element	Charges	n	Element	Charges
1	C	-0.114	19	H	0.066
2	C	-0.096	20	H	0.051
3	C	-0.363	21	H	0.042
4	C	0.530	22	H	0.072
5	C	-0.274	23	H	0.088
6	C	-0.143	24	H	0.135
7	C	-0.837	25	H	0.217
8	C	0.774	26	H	0.191
9	C	-0.129	27	O	-0.453
10	N	-0.840	28	O	-0.556
11	H	0.341	29	H	0.400
12	H	0.351			
13	H	0.159			
14	H	0.019			
15	H	0.077			
16	H	0.084			
17	H	0.094			
18	H	0.114			

3. Results and discussion

3. 1. Molecular Modeling

The primary orientation of gabapentin anions in the interlayer space depends on the space obtainable for guest anions within the interlayer region. The d_{003} value of Zn_2Al-LDH determined by molecular modeling indicates that the gabapentin anion has available space in the interlayer space with a value set at 6.44 Å. Fig. 5 shows that due to the longitudinal van der Waals radius of gabapentin molecules, equal to 7.34 Å, there is not enough free space for guest anions to be placed vertically concerning the horizontal layers of LDH. Therefore, the initial optimization showed that the anions tended to be placed horizontally between the layers. Fig. 5 also shows the cross-sectional view of the primary orientation in the supercell for gabapentin molecules in the interlayer space of Zn_2 Al-LDH.

3.2. Experimental and calculated XRD comparison

The combination of experimental XRD results and molecular simulation provides valuable insights into the structural arrangement of gabapentin -Zn_2Al-LDH guest anions within the interlayer space. By analyzing the water content and the positioning of water molecules in the interlayer space, as well as the orientation of the guest anions, researchers can accurately interpret X-ray diffraction patterns. This alignment between calculated and measured XRD data enhances our understanding of the molecular interactions at play in this system. Fig. 6 shows the molecular dynamics simulation results

calculated for the experimental XRD patterns of gabapentin-Zn_2Al-LDH [47].

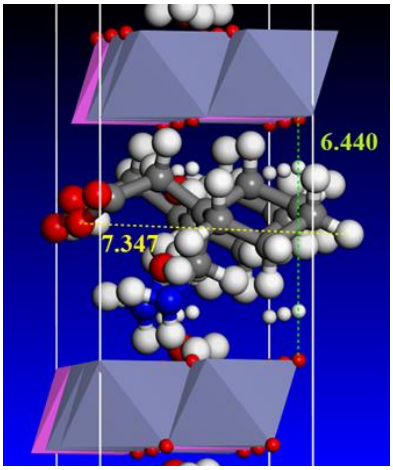

Fig. 5. Initial orientation of guest anions inside the interlayer space of Gabapentin - Zn_2Al-LDH

The experimental XRD pattern (previous work) for d_{003}, d_{006}, and d_{009} was observed at the maximum peaks of 8.74Å, 4.42 Å, and 3.01 Å, while the calculated XRD pattern is observed at 8.74Å, 4.36 Å, and 2.91Å, respectively. The slightly higher value of the experimental value of d_{009} compared to the calculated value of d_{009} can be due to the effect of the crystal size on the width of the peaks and can also be due to the irregularities of the guest anions in the structure, which is ignored in the software [48]. The experimental XRD anisotropic peak width is caused by the non-spherical and non-crystalline structures of gabapentin -Zn_2Al-LDH. Other factors such as residual stress, crystal structural defects, and machine error can also contribute to network deformation, which in turn causes the peak to shift. These factors are somewhat common in the solid state [49].

3.3. Molecular dynamics profiles of Gabapentin - Zn_2Al-LDH

Fig. 7 shows parts a and b picture of the equilibrium structures of the gabapentin- Zn_2Al-LDH system, before and after molecular dynamics simulation. Note that before the simulation, the gabapentin and water molecules were randomly placed between the layers. By analyzing the output files of molecular dynamics calculations (trajectories), the equilibrium of simulation systems exposes the arrangement of gabapentin anions.

3.4. Angle Distribution

The angular distribution of the molecules (molecular dynamics) was used to describe the orientation of gabapentin molecules within the LDH layer using the output file generated from the Zn_2Al-LDH simulation. The direction of the gabapentin anion

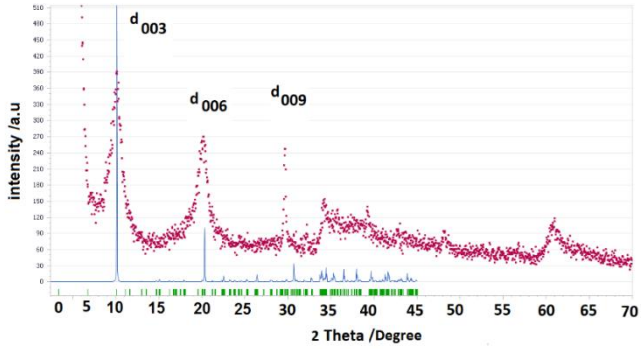

Fig. 6. The comparison between the X-ray diffraction patterns of a nanohybrid gabapentin - Zn_2Al-LDH. The blue peak represents the calculated data, while the dotted red peak represents the experimental data

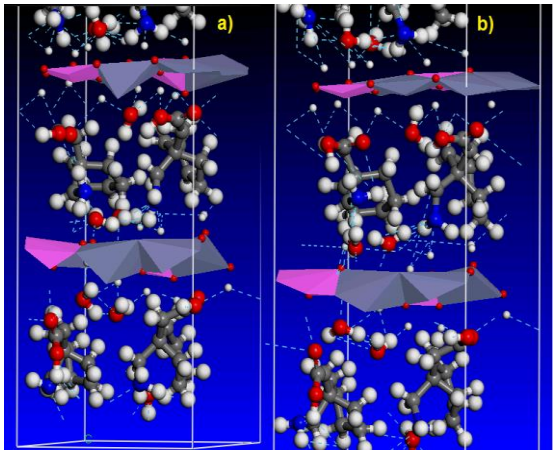

Fig. 7. Image of balanced structure, a (before) and b (after) resulting from trajectory files of molecular dynamics simulation of Gabapentin - Zn_2Al-LDH

tail vector was calculated considering the perpendicular direction to the midplane (XY) of the plane. This is defined as a tail vector between the C atom of the carbonyl group and the O atom of that acidic part, which is connected.

3.4. Angle Distribution

The angular distribution of the molecules (molecular dynamics) was used to describe the orientation of gabapentin molecules within the LDH layer using the output file generated from the Zn_2Al-LDH simulation. The direction of the gabapentin anion tail vector was calculated considering the perpendicular direction to the midplane (XY) of the plane. This is defined as a tail vector between the C atom of the carbonyl group and the O atom of that acidic part, which is connected.

The angle(θ) between the tail vector and the perpendicular vector to the layer surface of the Zn_2Al-LDH system is shown in Fig. 8. These calculations show that the longitudinal axis of gabapentin molecules in the interlayer space is located with a slope of 90.56 degrees (horizontally inclined) from the direction

perpendicular to the LDH layers. Fig. 9 shows the most likely placement of gabapentin molecules in the interlayer space. Gabapentin is inclined in LDH layers and the tail direction of gabapentin molecules is tilted at an average angle of 85 to 95 [50].

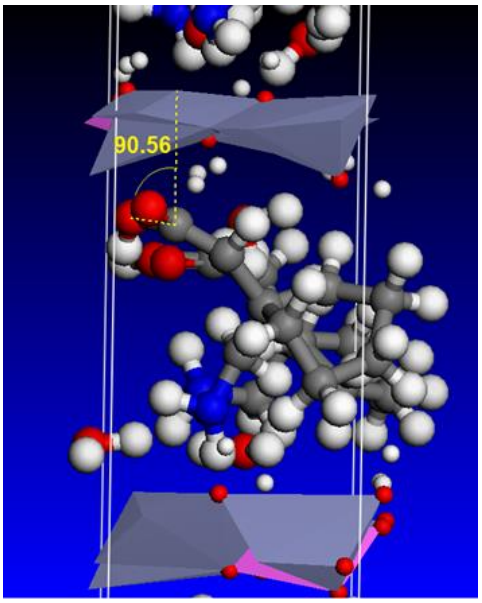

Fig. 8. The angle between the tail vector of Gabapentin molecules with the lamellar surface of LDH layers.

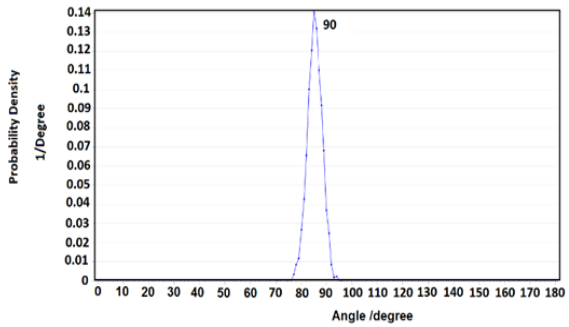

Fig. 9. Distribution of the slope angle (θ) of the tail vector of the Gabapentin molecule according to the normal interface.

3.5. Radial Distribution Functions

The interaction of end groups with water can be determined using the partial *radial distribution function* (RDF), which describes the number of A-type atoms located at an average distance r from B-type atoms [45]. RDF dependence of water molecules on end groups of gabapentin molecules were calculated with molecular dynamics time steps of 1000 ps. As you can see in Fig. 10, water molecules are scattered inside the interlayer space around the end groups, and they can be separated into two accumulation layers that are positioned at certain distances from the end groups of gabapentin (1 and 2.1Å). Most water molecules are closely related to OH^- of LDH layers and the COO^- group of guest molecules.

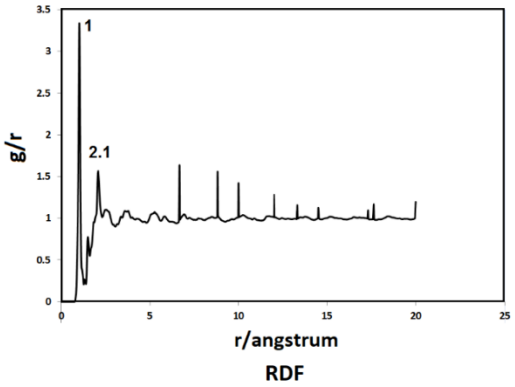

Fig.10. RDFs between end groups of Gabapentin and water molecules between LDH layers.

3.6. Mean Square Displacements

To investigate the stability, immobility, and actual delivery of gabapentin molecules when LDH is used as a carrier, we calculated the mean square displacements (MSDs) for gabapentin and water molecules after a total computational time of 500 ps and step time equal to 0.5 fs through the molecular dynamics output file. MSD analysis provides significant information about of the gabapentin stability in the LDH layer. The system has reached equilibrium as indicated by the consistent slope of the MSD curve over time. Figure 11 displays the mean square displacement (MSD) of two distinct molecules during 1000 ps of molecular dynamics simulations. MSD is attained from *Equation 1* [51].

$$\mathbf{MSD(t)} = \left\langle \frac{1}{N} \sum_{i=1}^{n} [\mathbf{ri(t)} - \mathbf{ri(0)}]^2 \right\rangle \quad (1)$$

The number of target molecules is represented by N and $r_i(t)$ indicates the position of molecule i at a specific time t. The well-known *Einstein relation* [eqn (2)] allows for the determination of the diffusion coefficient (D).

$$D\alpha = \frac{1}{2dN\alpha} \lim_{t\to\infty} \frac{d}{dt} \left\langle [\mathbf{ri(t)-ri(0)}]^2 \right\rangle \quad (2)$$

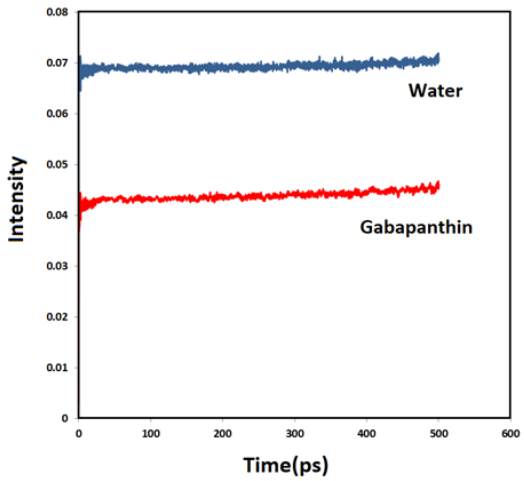

Fig. 11. Comparative calculations of MSD for Gabapentin and water molecules inside the Gabapentin-Zn_2Al-LDH hybrid

3.7. Total energy profile analysis of gabapentin - Zn_2Al-LDH

Here, the target is the structure of the aggregated molecules, where the anions of gabapentin are introduced into the LDH. The simulation is done using the smart minimizer proceeding to minimize the optimization of the structure. The minimized system was used to adjust the length and angle of the equilibrium bonds. At room temperature (298 K), a statistical NPT ensemble was utilized to simulate molecular dynamics. The time step was 0.5 fs and the total simulation time was 1000 ps. A steady state of potential energy is attained in Fig. 12, following a simulation time of 1000 ps, with the last 1000 ps used for analysis.

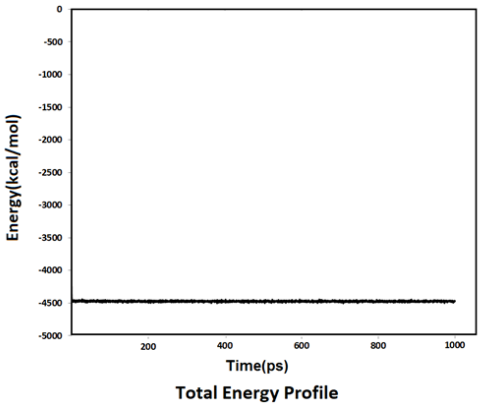

Fig. 12. The total energy profile time of the Gabapentin -Zn_2Al-LDH.

3. 8. Molecular orbital analysis for Gabapentin

From Fig. 13, It can be seen that the HOMOs are mostly on the N atoms of the amine group and the methylene carbon adjacent to the amine group and the LUMOs include two non-uniform orbitals, mostly on the carbon and oxygen atoms of the carboxylate group and partly on the carbons of the methylene group adjacent to the carboxylate group have been distributed.

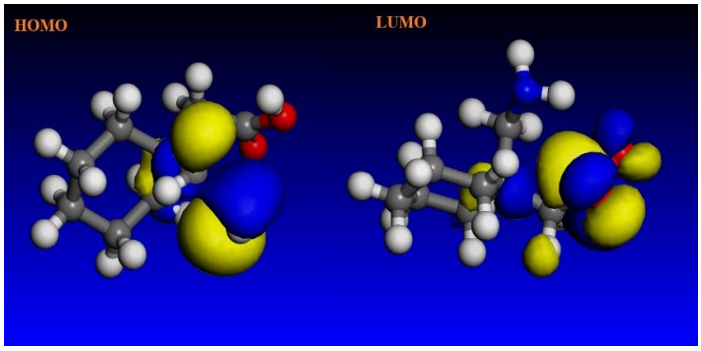

Fig. 13. The HOMO and LUMO shapes calculated by the DFT-PBE method for a Gabapentin molecule.

These results show that the nitrogen atoms of the amine group and the methylene carbon adjacent to the amine group of the gabapentin molecule play an important role in the oxidation, and loss of electrons inside the LDH layers. Also, the LUMO molecular orbitals show that the carbon and oxygen atoms of the carboxylate group and to some extent the carbons of the methylene group adjacent to the carboxylate group in the gabapentin compound play the role of electron acceptors in the electron exchange between the gabapentin drug and LDH layers.

4. Conclusion

Gabapentin is a type of anticonvulsant drug used to treat paroxysmal seizures, neuropathic pain, hot flashes, and restless legs syndrome. When drugs are released quickly in the body and have a short duration, the body can develop resistance to them. However, when gabapentin is released slowly and continuously through the interlayer space of Zn_2Al-LDH, resistance is less likely to occur. Research on the synthesis and investigation of double-layered hydroxide compounds with simulation calculations for large organic anions has been limited. This study focused on modeling the placement of gabapentin in the interlayer space of Zn_2Al-LDH and conducting molecular dynamic simulations to study how the drug is absorbed and released. The study began with quantum simulation to determine the partial charge of the drug, followed by classical mechanics calculations to optimize the structure of the drug-Zn_2Al-LDH complex. The results of the molecular dynamic simulation showed that water molecules were released faster than drug molecules from the Zn_2Al-LDH hybrid structure. Additionally, characterization of the Zn_2Al-LDH nanohybrid indicated good agreement between experimental XRD data and simulated XRD data, with the drug molecules being distributed relatively horizontally.

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