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Molecular dynamics simulation of entecavir-silver nanoparticles at different biological pH

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Abstract: Entecavir is a well-known antiviral drug, commonly prescribed for the treatment of hepatitis B and showed promising therapeutic effects against HBV polymerase. The replication of Hepatitis B Virus requires HBV-DNA polymerase and its natural substrate is deoxyguanosine triphosphate. Entercavir inhibit its activity by phosphorylating into its active metabolite. Furthermore, the efficiency of silver nanoparticles as an antimicrobial or antiviral agent is known for centuries. This study focused on the *in-silico* stability studies of silver nanoparticles of entecavir. The silver nanoparticles of entecavir synthesized by previously reported method. The stability of drug metal complex was predicted by analysis of variations in internal energies including potential energy, kinetic energy and different non-bonded energies during the simulation run of 4000 picoseconds of different molecular systems. After the simulation run it was concluded that the molecular systems of drug metal complex in aqueous solution at pH 4 showed greater instability as compared to the pH 2 and 6.9. This research gives the idea about the significance of molecular dynamics simulation technique in the field of pharmaceutical sciences for the analysis and characterization of pharmaceutical products and visualizes the effects of different environmental parameters on the structure and physicochemical properties of drug molecules.

Keywords: Entecavir, nanoparticles, MD simulation, pharmaceutical analysis, computational chemistry.

INTRODUCTION

The potential of silver nanoparticles in the field of medical sciences is known for centuries. The stability study of metallic nanoparticles of silver complexed with antiviral enables the researchers to understand the thermodynamics and structural characterization of metallic drug, influenced under different biological conditions. Unlike other metals, silver showed promising antimicrobial characteristics solely and in complexation with other antimicrobials and its exceptional structural properties can also influence the bioavailability and physicochemical properties of antimicrobial drugs (Alexander 2009; Bharathi *et al*., 2018; Kemp *et al*., 2009; Netala *et al*., 2016).

The *in-silico* characterization of metal drug complex by the technique of molecular dynamics simulation, which interprets the classical Newton's equation of motion to analyze trajectories, movements and interactions of given molecular system at the atomic level (Reges *et al.*, 2017; Shim and MacKerell Jr 2011; Feig *et al*., 2011; de Ruiter and Oostenbrink 2011; Gallicchio and Levy 2011), predicts the structural and dynamical characteristics of metallic drug nanoparticle. Molecular dynamics simulation is an *in-silico* technique that analyzes and visualizes any system of molecules at atomic level (Wu *et al*. 2021; Liu *et al*. 2021; Mosavi *et al*. 2021) and predicts the possible interactions of atoms on the bases of different interaction energies involve in the system (Sun *et al*. 2018; Xue *et al*. 2022). These interaction energies, including bonded and non-bonded energies, can analyze to predict the stability of molecular system in that particular environment. Moreover, this technique is reported as one of the most efficient method to understand the chemistry of proteins and macromolecules (Hata 2020; Geng *et al*., 2019; Singh *et al*., 2018; Wang 2021; Mokaberi *et al*., 2021) and serve as a significant tool in drug discovery through mechanistic drug design (Liu *et al*., 2018; Ibrahim *et al*., 2020; Lee *et al*., 2019; Huynh 2020). However, the physicochemical properties of potential drug molecules and different metal complexes can also be predicted through this technique, without the involvement of any binding proteins and biological molecules (Li *et al*., 2021; Mamatkulov and Schwierz 2018; Rbaa *et al*., 2020). Multiple studies of molecular mechanics MD simulation of silver metal complexes and nanoparticles have been reported which elaborated the thermodynamics and structural characteristics of metal complex to predict the stability of molecular system in different environments (Tian 2008; Alarifi *et al*., 2013; HA *et al*., 2013; Chen 2017; Martin *et al*., 2019). Sohraby performed MD simulation of silver nanoparticle in order to theoretically estimate the potential of rosemary active compounds in coating of nanoparticles and analyze the

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dynamic behavior of these compounds with silver nanoparticles (Sohraby *et al.,* 2020). Previous study reported different shapes of silver nanoparticles by interpreting the influence of temperature and binding energy by using polarization effects of different force fields in MD simulation (Blazhynska 2018; Blazhynska 2019). In MD simulation the atoms and molecules within the molecular system are allowed to simulate for a fixed period of run time and their internal energies and forces within the molecules analyzed by the interpretation of molecular mechanics force field. Force fields are basically the expression of parameterized empirical energy, involved in the interactions at atomic level of molecular systems and depending upon the nature of system it can be varied (Krieger *et al*., 2004; Monticelli and Tieleman 2013). In any force field the potential energy between the particles is described in functional form of bonding potential and non-bonding potential. Hook's law expressed the potential energy function of bonding potential (Vanommeslaeghe and MacKerell Jr 2012) and non-bonding potential are independent of any physical bonding and described by Leonard-Jones potential as weak Van der Waal and electrostatic interactions (Paton and Goodman 2009). In this study the variations in these different internal energies of potential energy function of MD simulation, are observed to predict the stability of concerned metallic nanoparticle in different biological environment.

As most of the drugs are weak acid or weak base, their thermodynamics, physicochemical and pharmacological properties can greatly influence by the pH of environment. The pharmacokinetics of metallic drugs or nanoparticles significantly depends on pH of medium of different body fluids and the number of studies has been reported on the effect of pH on metallic nanoparticles (Jeevanandam 2019; Zhang 2010; Madhusudhan *et al*., 2014; Chitra and Annadurai 2014). A study reported in 2013, elaborate the influence of variation in physiological pH of biological medium on the antifungal activity of silver conjugated with the nanoparticles of antifungal drugs (Singh *et al*. 2013).

The prevalence of hepatitis-B is still challenging to control for healthcare providers and the advancements in pharmacotherapy is still the prime goal for many researchers and research institutes. The therapeutic outcome of guanidine analogues in the treatment against hepatitis B virus (Fu *et al*., 2014) polymerase, is quite promising especially the activity of entecavir. Several studies reported that entecavir is more effective in reduction of HBV DNA than lamivudine (Tassopoulos 2001) as well as reduction of incidence of hepatocellular carcinoma is seen in patients treated with entecavir therapy (Colonno *et al*., 2001). After considering the history of antimicrobial activity of silver metal, it is proposed that the synthesis of nanoparticles of entecavir complexed with silver metal can significantly enhanced the efficacy and antiviral activity of entecavir.

In this study the stability of synthesized nanoparticles of entecavir-silver complex (Shoaib *et al*., 2021) was analyzed by *in-silico* MD simulation technique while protonating the molecular system in different biological pH. Entecavir is a weak base in nature and the variation in pH of physiological environment can also greatly influence the structural properties, drug delivery on target site, stability and pharmacokinetics of entecavir-silver nanoparticles. Previous study reported the instability of entecavir in acidic medium (Desai *et al*., 2007). The stability of this metal complex predicted by the interpretation of each correlation plots obtained and analyzed from the database tabulated after the 4000 picosecond MD simulation run of four molecular systems of entecavir-silver complex in aqueous medium of different biological pH.

This study was designed and performed to predict the physical and chemical stability of metallic complex of Entecavir drug, using *in-silico* molecular dynamics technique. The results obtained from this study could be beneficial for the development of dosage form and pharmacokinetics profile of silver-entecavir metallic complex.

MATERIALS AND METHODS

In this study, structure of previously synthesized metallic nanoparticles of entecavir complex with silver metals was analyzed by *in-silico* molecular dynamics simulation. Structure preparation, optimization of molecular system, energy minimization and MD simulation of drug metal complex was done by MOE 2018.0801.

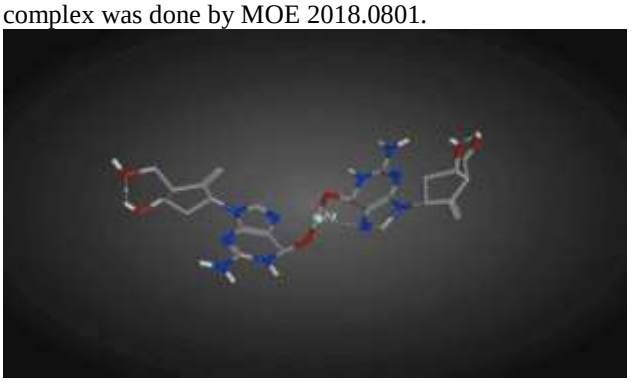


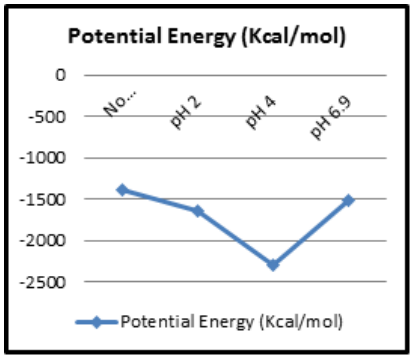
Fig. 1: Energy Minimized Structure of Entecavir-Silver.

Structure Preparation and Optimization of Molecular system

MOE 2018.0801 used for structure preparation of synthesized silver-entecavir nanoparticle.

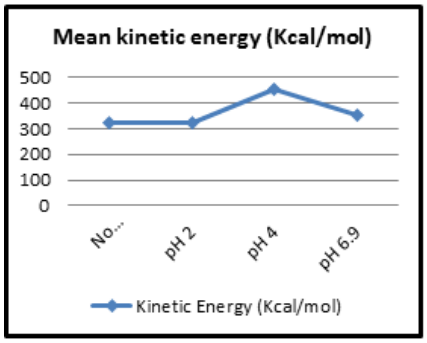
Using force field MMFF94x (Zhu 2014) whole molecular system energy minimized to most stabilized spatial orientation of metal complex (fig. 1). The partial charges

Table 1: Comparative graphical analysis of mean potential energy at all different pH.



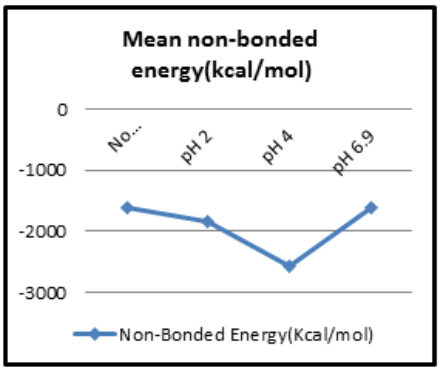
pH	Mean Potential Energy (Kcal/mol)
No protonation	-1385.16
pH 2	-1637.74
pH 4	-2296.26
pH 6.9	-1523.93

Table 2: Comparative graphical analysis of mean kinetic energy at all different pH.



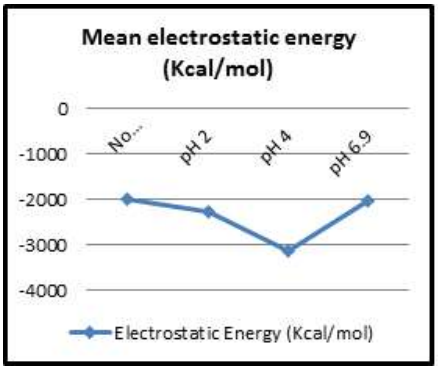
pH	Mean Kinetic Energy (Kcal/mol)
No protonation	322.843
pH 2	324.001
pH 4	455.933
pH 6.9	353.914

Table 3: Comparative graphical analysis of mean non-bonded energy at all different pH.



pH	Mean non-bonded energy(Kcal/mol)
No protonation	-1600.03
pH 2	-1852.15
pH 4	-2559.44
pH 6.9	-1621.48

Table 4: Comparative graphical analysis of mean electrostatic energy at all different pH.



pH	Mean electrostatic energy (Kcal/mol)
No protonation	-1978.69
pH 2	-2271.92
pH 4	-3128.02
pH 6.9	-2017.28

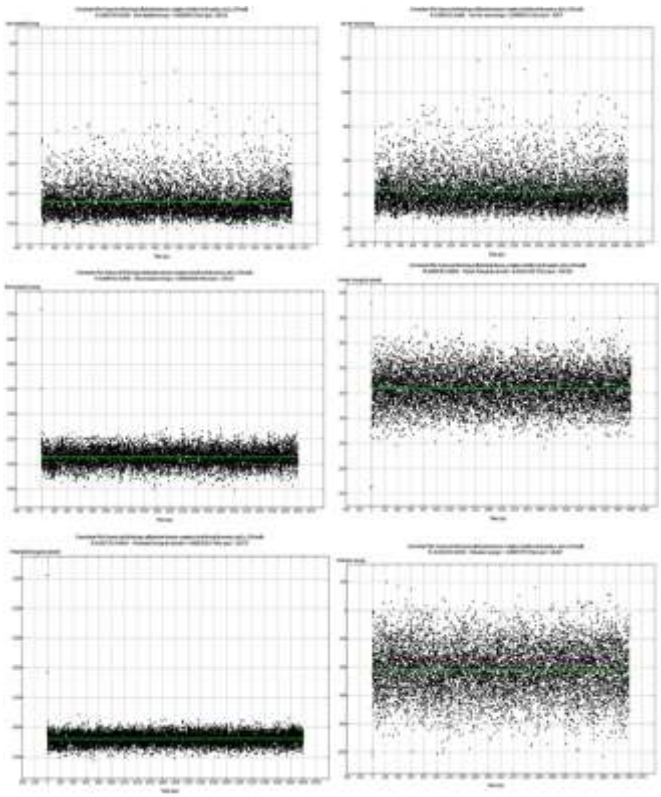


Fig. 2: Correlation Plots at pH-2 of Potential Energy, Kinetic Energy, Non-Bonded Energy, Electrostatic Energy, Van Der Waal Energy and Solvation Energy against Runtime of MD Simulation in PS. Each Dot Represents Single Value At Every 0.5ps and Line Indicates Average of Respective Internal Energy.

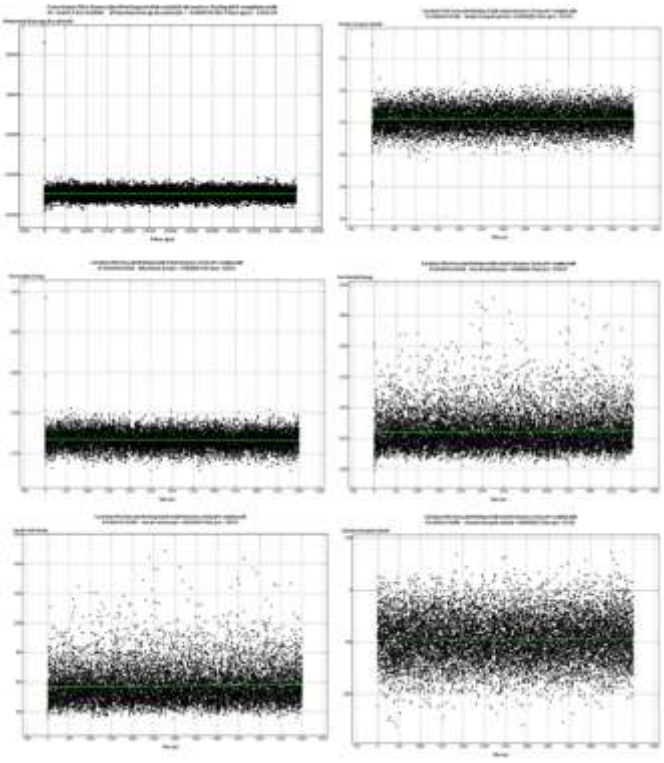


Fig. 3: Correlation Plots at pH-4 of Potential Energy, Kinetic Energy, Non-Bonded Energy, Electrostatic Energy, Van Der Waal Energy and Solvation Energy against Runtime of MD Simulation in PS. Each Dot Represents Single Value At Every 0.5ps and Line Indicates Average of Respective Internal Energy.

applied using the same force field. In order to change the pH, whole system was protonate using Protonate 3D tool met the desired pH i.e. 2, 4 and 6.9. Keep the temperature constant at 300 Kelvin. Set the electrostatic functional form to "GB/VI" that indicates Generalized Born Volume Integral Formalism which is basically the function of Born Self Energy (Vollick 2005).

MD simulation

Before starting the simulation, algorithm was set to Nose Poincare Andersen equation (Sturgeon and Laird 2000). These are equation of motion that will be solved and represent the properties of any physical system with respect to its motion as a function of time. The force field set to MMFF94x then solvate the molecular system by defining the periodic boundary condition of spherical shape and water molecules added as the solvent.

Margin was set to minimum which is the specified distance of solvent molecule from solute atom. Now the MD simulation run and the system was subjected for equilibration run of 1000ps and 3000ps for production run of total 4000ps of simulation run within protocol. After the completion of simulation, the entire database was tabulated in .mdb format file. This database included different internal energies and thermodynamic descriptors. Correlation plots were generated from the database for each descriptor of molecular system of all different pH. Comparative study of variation in internal energies or descriptors of Entecavir-Silver complex, at different protonation states (pH) predicts the stability of metal complex.

RESULTS

In the analysis, data of 4000 picosecond MD run of Ent-Ag complex at different protonation states was tabulated computing the values of internal energies or descriptors of molecular system, at every 0.5 picosecond up to 4000 picoseconds. The descriptors include the state of simulation either it is in equilibration phase or production phase, time of simulation in picoseconds, Hamiltonian representing the total energy acting on each particle involve in the system, potential energy of the system, kinetic energy of the system, temperature of the system, pressure on each particle involve in the system, volume of the sphere that is kept constant, bond stretch energy of the system, solvation energy, angle bend energy, electrostatic energy, non-boned energy and Van der Waal energy. Correlation plot of internal energies and thermodynamic parameters have been plotted against simulation run time and the variation in these parameters predicts the stability of drug-metal complex in all different environments. Internal energies include potential energy, non-bonding energies, electrostatic energy, Van der Waal energy, solvation energy and kinetic energy. In correlation graph every single dot indicates the value of respective parameter at that time of MD run and the line between the dots indicate the average value of respective parameter in whole MD run of 4000 ps.

MD Simulation of molecular system protonated at pH-2,pH-4, pH-6.9 and without protonation

The whole systems treated with 3D protonation and adjust the environment of drug metal complex at different protonation states then run the MD simulation to get the data and correlation plots of internal energies at pH-2 (fig. 2), pH-4 (Fig. 3) and pH-6.9 (Fig. 4) and a system without protonation (fig. 5)

Analysis of internal energies in Correlation Plots

The data obtained from the correlation plots of MD simulation composed of the values of energies that are involve in the system during the whole run of 4000 picoseconds of MD simulation including the equilibration run time and production run time. These values calculated at every 0.5 picosecond interval of MD run. So the finalized data is consisting of substantial number of values that are all plotted in correlation graphs. Analysis of this data was done by plotting the mean values of energies in all four systems of different protonation states.

DISCUSSION

Mean potential energy

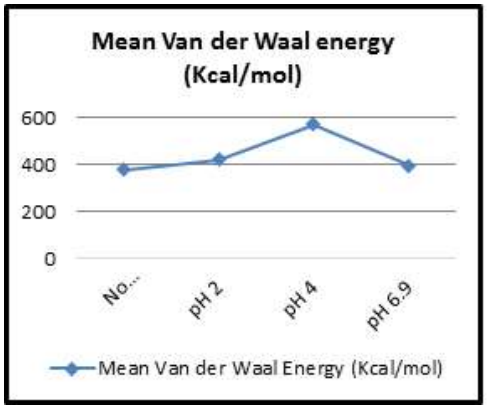
The theoretical background of molecular dynamics based on molecular mechanics and uses the same potential energy equation (Vanommeslaeghe and Guvench 2014; Kondepudi 2008). The final correlation plots of potential energy (Table 1), compares to predict the stability of drug metal complex in same molecular systems protonated at different pH. Comparison graph of average potential energy gives the idea that the Entecavir-metal complex is least stable at pH 4 showing higher negative average potential energy then at other pH with great margin and slightly higher negative average potential energy at pH 2. By comparing the average potential energy of the system with no protonation, it could be concluded that the introduction of pH effect, by protonation in MD simulation, has greatly influence the potential energy of the molecular system (Suh 2008; Levitt *et al*. 1995).

Mean Kinetic Energy

The whole data obtained after MD simulation was calculated statistically by the force fields applied and these force fields totally depends on potential energy rather than kinetic energy (Laio and Parrinello 2002). The comparison graph of average kinetic energies in all molecular systems of same configuration and different pH (table 2) is only significant to prove that the systems are physically valid.

The plot showed very minor variation in average kinetic energy in all three different pH and also the average

Table 5: Comparative graphical analysis of mean Van der Waal energy at all different pH.



pH	Mean Van der Waal energy (Kcal/mol)
No Protonation	378.661
pH 2	419.77
pH 4	568.575
pH 6.9	395.799

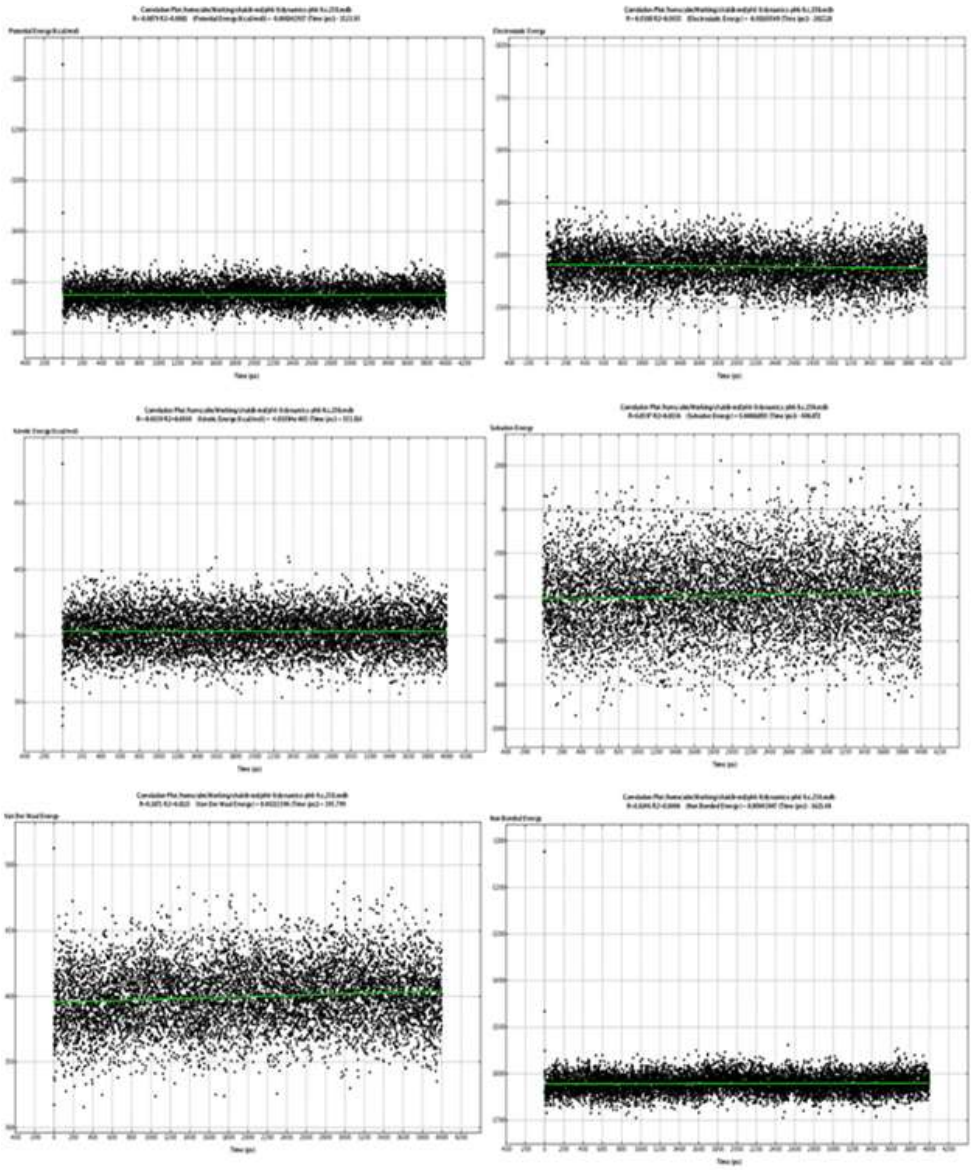
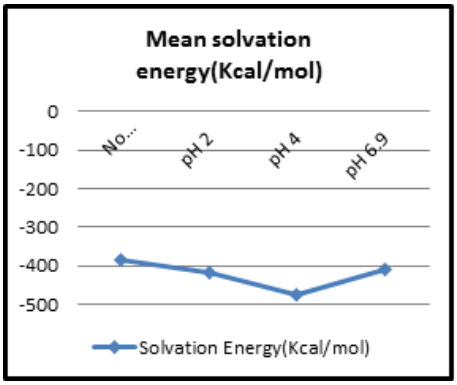


Fig. 4: Correlation Plots at pH-6.9 of Potential Energy, Kinetic Energy, Non-Bonded Energy, Electrostatic Energy, Van Der Waal Energy and Solvation Energy against Runtime of MD Simulation in PS. Each Dot Represents Single Value At Every 0.5ps and Line Indicates Average of Respective Internal Energy.

Table 6: Comparative graphical analysis of mean solvation energy at all different pH.



pH	Mean solvation energy(Kcal/mol)
No protonation	-386.373
pH 2	-416.617
pH 4	-475.011
pH 6.9	-408.072

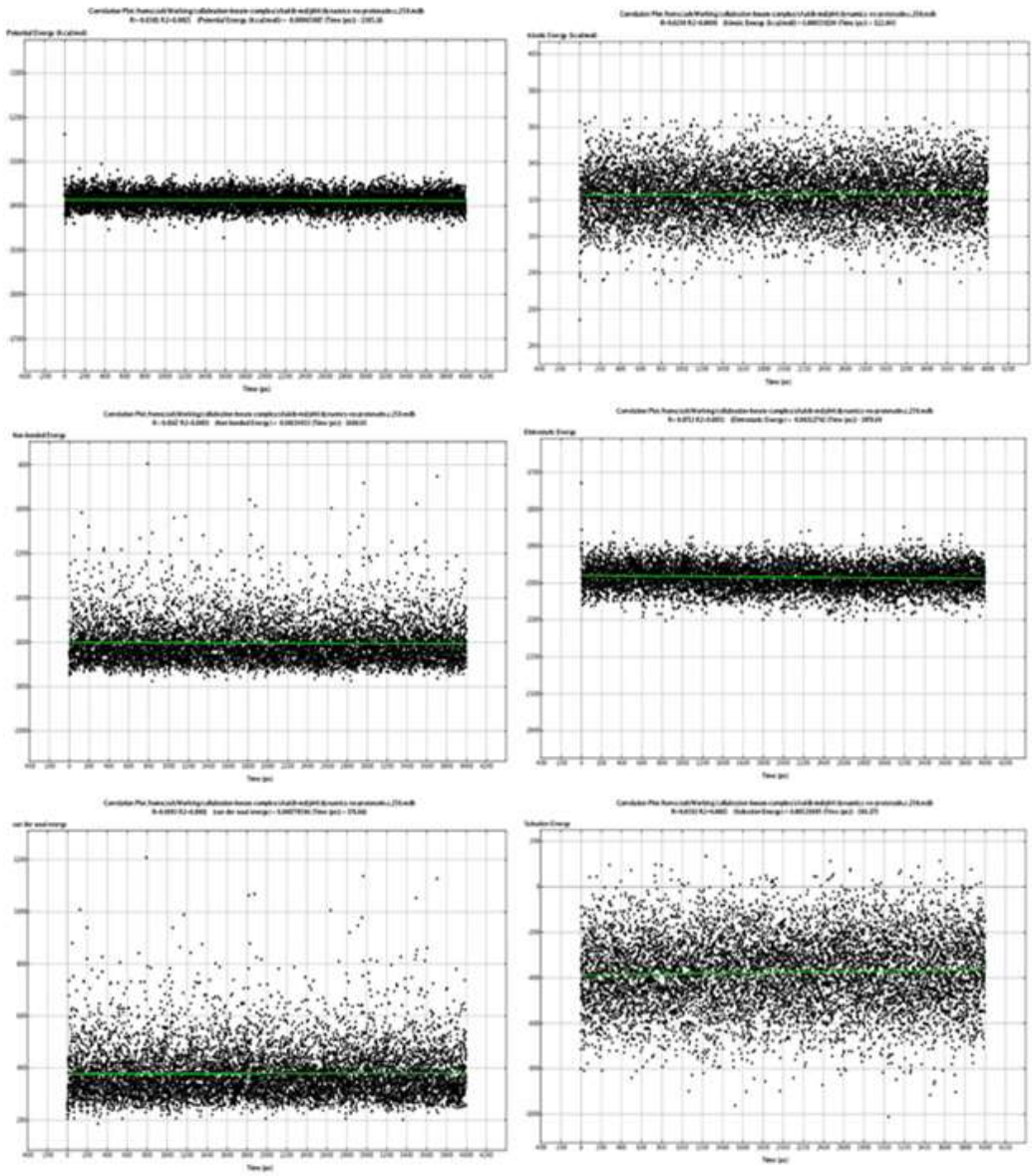


Fig. 5: Correlation Plots for system of without protonation, of Potential Energy, Kinetic Energy, Non-Bonded Energy, Electrostatic Energy, Van Der Waal Energy and Solvation Energy against Runtime of MD Simulation in PS. Each Dot Represents Single Value At Every 0.5ps and Line Indicates Average of Respective Internal Energy.

kinetic energy of system without protonation is almost similar to the values obtained after the introduction of pH effect by protonation. These variations are basically because of change in internal temperature of molecular system. This predicts that the systems are physically valid in all MD simulation run.

Mean Non-Bonded Energy

Non-bonded energies in the system reflect the non-covalent interactions with in the drug-metal complex and also in between solvent and drug-metal complex. Electrostatic energy and Van der Waal interactions also included in non-bonded interactions and they are responsible in maintaining shape and stable configuration state of metal complex in medium (JE 1994). Comparison study of average electrostatic energies in all systems (table 3) predicted that the entecavir-silver complex is most unstable at pH 4 then at pH 2 then other protonation states. Result of non-bonded energy data is similar to the potential energy analysis, sympathizing that entecavir-silver complex is least stable in acidic medium (JE 1994).

Mean electrostatic energy

The configuration and geometry of charged metal complexes significantly influenced by the electrostatic interactions involved in the system within the molecule or with the solvent molecules (Stote and Karplus 1995). During the optimization before MD simulation, partial charges applied to whole system that leads to the involvement of electrostatic energy. Comparison data of average electrostatic energy in all different pH (table 4) showed higher negative electrostatic energy at pH 4 and at pH 2, this predicts the unstable electrostatic interactions at acidic pH as compared to neutral pH and system without protonation.

Mean Van der Waal energy

The electromagnetic attractive and repulsive forces generate due to the electron clouds around molecules leads to non-bonded weak Van der Waal interactions (Canter 2016). These Van der Waal interactions are distance dependent weak forces by which a molecule interacts with its surrounding molecules or medium and maintain its shape and these forces significantly influence by the thermodynamic properties of molecule and whole system (Murthy 2006). Van der Waal energy is resulted from very weak forces of interactions and the results obtained by the comparison of average Van der Waal energy in all different pH (Table 5) shows minor difference. Similar to the other non-bonded energies and potential energy, average Van der Waal energy comparison data also represents higher energy at pH 4 than any other protonation states predicting the instability of system in acidic medium.

Mean solvation energy

Solvation free energy has crucial impact on the stability and thermodynamics properties of molecular systems (Shi *et al*., 2014). The solvation free energy is the non-bonded interaction between solvent and solute molecules. The structure and physicochemical properties of solute or drug molecule can be strongly influenced by the solvation energy and the variation in conformation and structural stabilities of solution of a drug molecule in different environments can be analyzed by the variation in solvation free energy (Rebertus 1979; Anandakrishnan *et al*. 2015). The average of solvation energies for all molecular systems of different pH is summarized (Table 6) and their comparative graph revealed the variations in solvation free energy by protonating the molecular system at different biological pH. From the results it can be concluded that the acidic pH is least favorable for ENT-Ag metal complex and the higher mean negative solvation energy at pH 4 showed instability of drug metal complex at pH 4.

CONCLUSION

The application of *in-silico* molecular dynamics simulation of entecavir-silver complex predicts the idea about the structural and thermodynamics stabilities in different pH. After the analysis of results obtained from the database of complete simulation run, it can be concluded that the variations in internal energies in all molecular systems of different pH gives the idea about the instability of drug metal complex in acidic medium. As these internal energies of molecular systems including potential energy, non-bonded energies, electrostatic energy and solvation energy are all responsible for every physicochemical and thermodynamics properties of matter. The major deviation of internal energies from the equilibrium was observed in the molecular system of pH 4 and then at pH 2. This also validates the previous study of experimental analysis of entecavir that reported the structural instability of the antiviral drug in a medium of pH 4 (Desai *et al*. 2007).

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