Assessing the molecular interaction between Poly lactic-co-glycolic acid (PLGA) 50:50 and Poly ethylene glycol in presence of Diethyl phthalate using in silico study - A novel approach of pre-formulation study

Abstract

The efficacy of a drug relies on drug formulation and targeting. Imatinib is an anti-cancer drug identified to be effective in the treatment of cancers like myeloid leukemia and lymphoblastic leukemia, and gastrointestinal tumors. The prediction of mixing energy and identification of docking interactions and scores can help identify the most efficient drug carrier/plasticizer molecule that could exert maximum pharmaceutical efficiency. The results of a preliminary study explicitly showed the potent carrier molecule before conducting formulation studies. Hence, the present study was designed to screen the interaction energies between different combinations of Poly (lactic-co-glycolic acid) (PGLA) or Poly Ethylene Glycol (PEG) or diethyl phthalate with Imatinib using *in silico* computational methods. The study results suggested that the binding energy and the score obtained for docking interactions for Imatinib versus diethyl phthalate was better when compared to the other combinations. Therefore, Diethyl phthalate might be a signature candidate to act as Imatinib-carrier/plasticizer. More formulation studies are warranted further to demonstrate the desired continuous drug release and maximum efficacy with Imatinib chemotherapy.

Introduction

Cancer prevalence is alarmingly increasing, and it is the second leading cause of death worldwide [1]. The pathogenic mechanisms of tumorigenesis have been explored by understanding the role of dysregulated proteins that potentiate cancer progression [2]. Protein tyrosine kinases act like biochemical switches which regulate the signalling cascades associated with metabolism, growth, differentiation and apoptosis in response to appropriate stimuli [3]. Dysregulation of tyrosine kinase activity plays a key role in cancer pathogenesis [4]. Tyrosine

kinases have ATP binding sites in their active sites, and the enzymatic activity transfers phosphate from ATP to tyrosine residues of certain cellular proteins [5]. Imatinib is a 2-phenyl amino pyrimidine derivative that acts as a tyrosine kinase inhibitor. Imatinib binds to the ATP binding site of tyrosine kinases and turns it into a closed and self-inhibited conformation [6]. Consequently, Imatinib inhibits the enzymatic activity of tyrosine kinases in a semi-competitive manner [7].

Imatinib is the first-line drug in the treatment of several cancers [8]. Apart from the revolutionary accomplishments in the management of Chronic Myeloid Leukemia (CML) [9], Imatinib showed promising results in treating gastrointestinal tumors, eosinophilic disorders,

Philadelphia chromosome positive acute lymphatic leukemia, bone marrow failure and steroid-refractory chronic graft versus host disease [10]. Celonib, Imalak, Lupitinib, Mesylonib, Mitinab are some of the brands of Imatinib available in the market [11]. After oral administration, the bioavailability of Imatinib was 90%, and C_{max} was achieved within 2-4 hours post-dose [12]. Increasing the Imatinib dose from 25 mg to 1000 mg eventually increased the mean area under curve (AUC) proportionally [13].

The recommended dose of Imatinib mesylate for adult patients in CML chronic phase is 400 mg/day (ref) and 600 mg/day for CML accelerated phase/blast crisis [14]. Imatinib is a wonder drug in the field oncology field. However, accomplishing sustained release and efficient delivery to the target site in Imatinib therapy is still challenging [15]. Hence, the present study was designed to analyze the mixing energy and interaction between Imatinib Mesylate and the polymers such as Poly (lactic-co-glycolic acid) (PLGA) 50:50 and Poly Ethylene Glycol (PEG) in the presence of the plasticizer "Diethyl phthalate" using *in silico* analysis to assess the possible conceptual explanation during the use of above formulation.

Methodology

Simulation platform for molecular interaction

In silico property analysis of formulation mainly applied two simulation elements, (a) "BIOVIA" material studio (Version 17.1.0.48), which is used for the geometric optimization and blends binding energy analysis [16]. (b) "BIOVIA" Discovery studio visualizer (Version 17.1.0.1643) has been applied for the interaction valuation between the polymers with the drug [17].

Optimization of geometry using forcite

The Forcite molecular mechanics tools are classically applied to optimise geometry for periodic systems of formulation complex. For the present study, 2D-structures of .sdf format of four combinations such as PLGA (50:50), PEG, Imatinib, Diethyl phthalate and the two solvents, namely, Isopropyl Alcohol (IPA) and Dichloromethane (DCM), were submitted to Forcite calculation. The Condensed-phase Optimized Molecular Potentials for Atomistic Simulation

Studies (COMPASS) force field were assigned with fine quality to calculate the initial and final potential energy of the components for each atom through summation of van der Waals and electrostatic properties; other parameters were default values [18].

Blends mixing

Blends protocol measure the binding energies and coordination number between the components of the formulation. The module calculates pair energy with the trajectories, and atom-based non-bonded interaction energies using 0.020 kcal/mol energy bin width. Further, the mixing energy is calculated using the following formula [19]:

$$E_{mix} = \frac{1}{2}(Z_{bs}\langle E_{bs}\rangle_T + Z_{sb}\langle E_{sb}\rangle_T - Z_{bb}\langle E_{bb}\rangle_T - Z_{ss}\langle E_{ss}\rangle_T)$$

Interaction analysis

Step by step analysis was carried out during each mix, and the molecular interaction was analyzed using Discovery studio. Bonded, non-bonded and non-favourable atom-based interactions and the complex formation during the formulation were analyzed [20].

Results and Discussion

Forcite energy profile for the components of the formulation

The protocol run of "Forcite" added four properties file in the results, which showed the energies of initial as well as final structure (Table.1). The run converted the molecule from the excited state (high energy) to the ground state (low energy) to make the molecule attain a stable configuration (Figure.1).

Table.1. Forcite energy profile of the formulation components

Molecule	Total Energy		RMS force	
	Initial Structure	Final Structure	Initial Structure	Final Structure
	Kcal /mol		Kcal /mol /A	

Dichloromethane (DCM)	1429.866	107.922	7.651E+002	8.886E-002
Iso Propyl Alcohol (IPA)	19219.496	-28.697	4.962E+004	8.365E-004
PLGA	6134.213	6.245	2.663E+003	8.558E+001
PEG	10656.383	-64.241	1.165E+004	5.639E-001
Imatinib	46795.549	0.936	1.806E+004	8.902E-002
Diethyl Phthalate	35249.845	20.811	3.313E+004	5.528E-004

From the profile of geometric optimization (Figure.1), it was observed that the energy of Imatinib initially started with 46795.549 kcal/mol and was brought to 0.936 kcal/mol in the 201st iteration step. The above change made the molecule attain its stable configuration by modifying its torsion angle. Similarly, the energies of all the components were minimized to local energy minima and subjected to blends analysis.

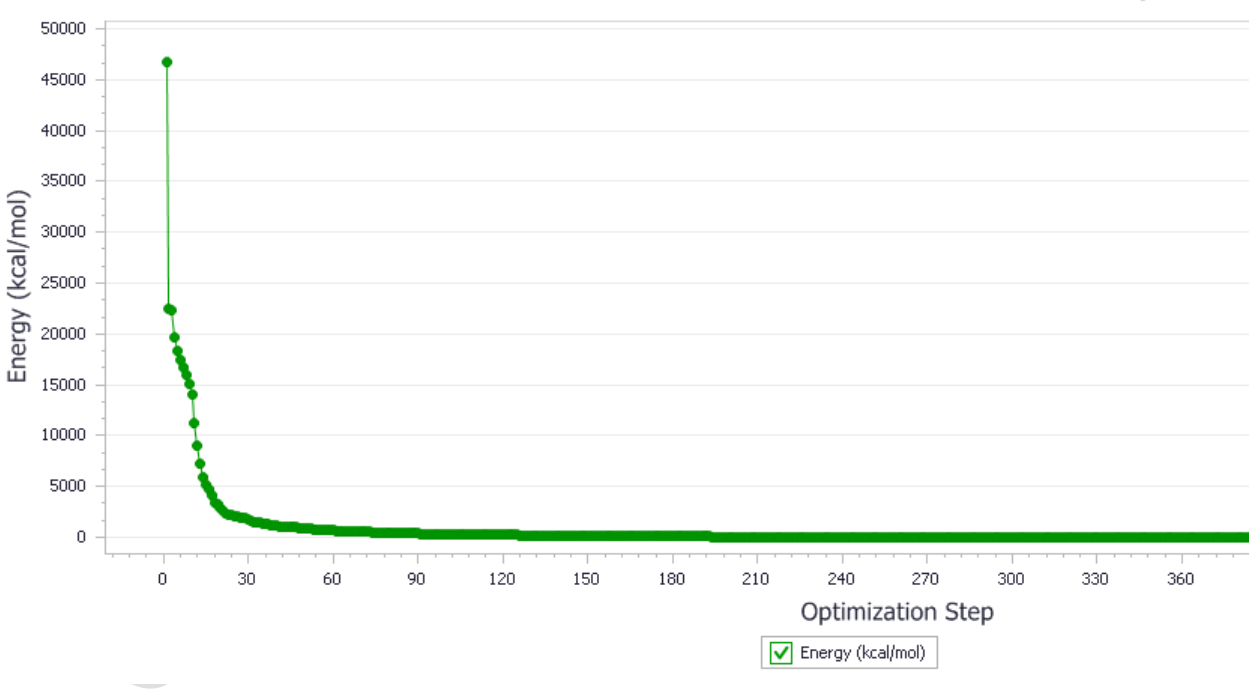

Figure 1. Geometric Optimization of Imatinib drug

Blends mixing

The compatibility of the binary mixture was calculated by combining the modified "Flory-Huggins model and molecular simulation techniques" [21]. The results of the protocol run revealed that the combinations of PEG-PLGA, PLGA-Imatinib and Imatinib-Diethyl Phthalate showed χ value of -9.6015, -1.2522, and -2.5806, respectively. The results indicated that the above-mentioned combination of the formulation would provide better results as compared to other combinations (Table 2). Similarly, the Emix value of the above mixtures was near Zero, which indicated the formation of a better formulation.

In general, a small or negative value of χ indicates that at this particular temperature, the two molecules have a favourable interaction. It is likely that at this temperature, a mixture of two components will show just one phase. If χ is large and positive, both the molecules prefer to be surrounded by similar components rather than each other. If the χ value is high enough, this contribution to the free energy overcomes the combinatorial entropy, and the mixture of the two components will separate into two phases [22].

Table 2 Blend mixing scores at temperature 298 K and mixing energy values of the components of the formulation.

Base	Screen	Chi (χ)-298 K	Emix
PEG	PLGA	-9.6015	-3.1452
PEG	Imatinib	26.4768	15.6792
PEG	Diethyl Phthalate	38.2390	22.6447
PLGA	Imatinib	-1.2522	-6.6634
PLGA	Diethyl Phthalate	12.6947	7.5176
Imatinib	Diethyl Phthalate	-2.5806	-1.5282

The possible mixture of the Base-Base, Base-Screen and Screen-Screen combinations are represented graphically (Figure 2). From the result, it was observed that Imatinib was used as a base, and Diethyl Phthalate was used as a screen. The mixing of all the combinations results in negative energy, which indicated that the above combination might be a better formulation.

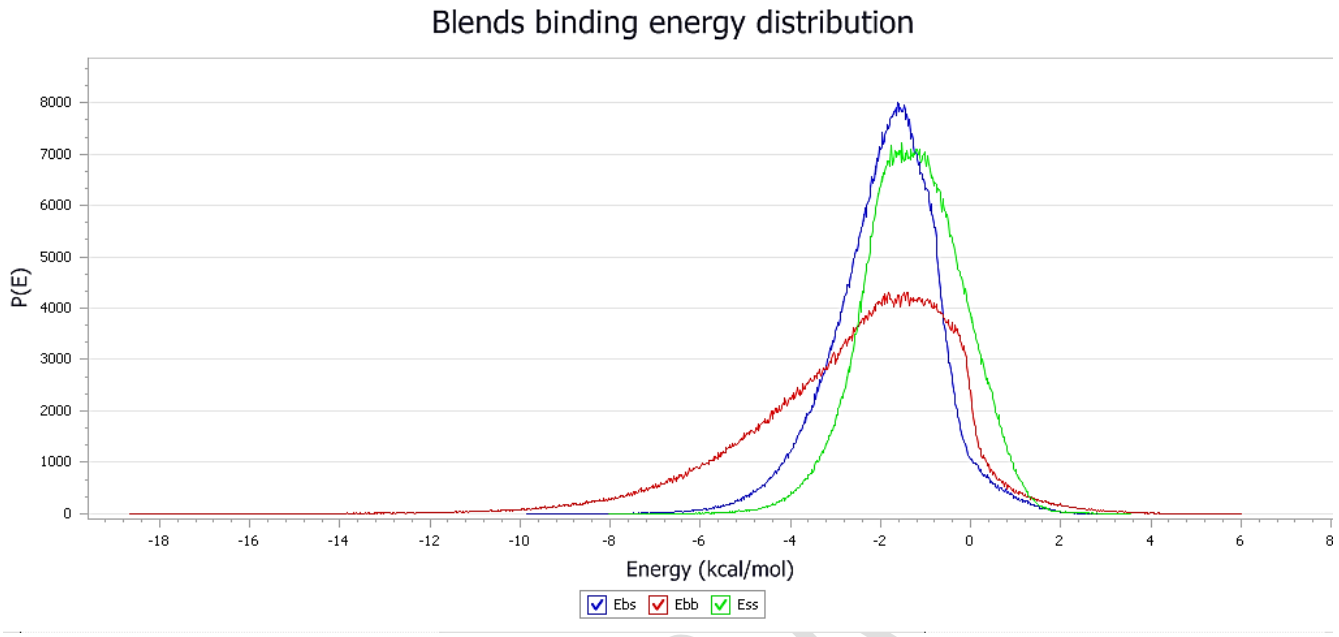

Figure 2. Blends binding energy distribution of Imatinib-Diethyl phthalate complex. Where, red, blue and green denotes the energy of the base-base, base-screen and screen-screen respectively.

Interaction pattern and interpretation

Imatinib and Diethyl phthalate exhibited a better interaction with each other. Phenyl ring of Diethyl Phthalate formed hydrophobic interaction with isolated di benzene ring of Imatinib. Also, the phenyl ring generated the π-alkyl interaction with the $–CH_2$ group of the diethyl phthalate (Figure 3).

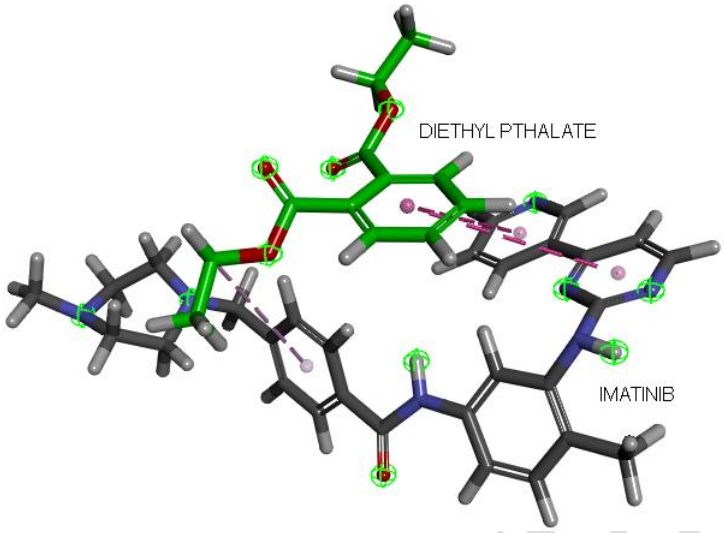

Figure 3. Interaction of Imatinib and Diethyl Phthalate

Similarly, the PLGA formed three conventional interactions with the Imatinib skeleton. Interestingly, the hydrogen atom in the benzene ring of the Imatinib formed a hydrogen bond with the esteric Oxygen of the PLGA molecule and the -CH2 group of the Imatinib generated ketonic (C=O) group of the PLGA (Figure 4) [24].

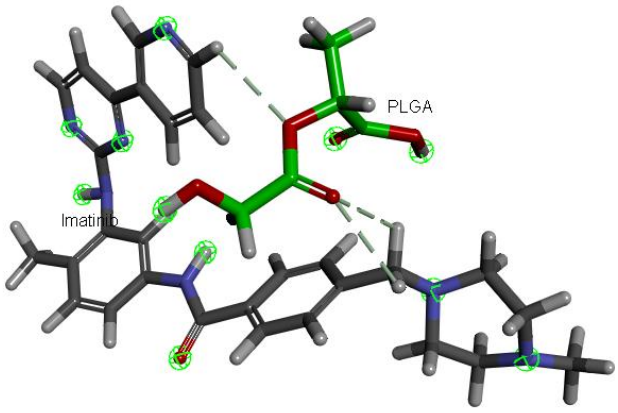

Figure 4. Interaction of Imatinib with PLGA

Conclusion

The combination of Imatinib and diethyl phthalate formulation is anticipated for the improved bioavailability through the extended-release into the circulation and at the target site of action. The results of the *in-silic*o experiments are evidence of the possibility

of using diethyl phthalate as an Imatinib carrier/plasticizer to increase the specificity of the formulation. Diethyl phthalate could be a promising candidate to attain effective delivery and target specificity of Imatinib in the treatment of different types of cancer and other diseases.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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