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| RESEARCH ARTICLE

Molecular Dynamics Prediction of the Solubility of Paracetamol in Polyethylene Glycol- Polylactide Copolymer Formulations

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| ABSTRACT
The poor dissolution profile of insoluble drugs such as Paracetamol (PCM) has been unbearable in the pharmaceutical industry. However, drug-polymer formulations are known to remedy this challenge. This study investigates the molecular dynamic prediction of the solubility/miscibility of paracetamol-polyethylene glycol-polylactide (PCM-PEG-PLA) copolymer formulation. Polymer chain analysis of various mole fractions of PEG and PLA monomers indicates that an increase in the concentration of PLA and a subsequent decrease in the concentration of PEG increases the copolymer solubility. The results also show that copolymerization of PEG increased the chain flexibility of the copolymers and the miscibility of the drug-copolymer formulation by enhancing the solubility of the copolymers. The mobility of the drug was investigated under NVE, NPT, and NVT ensembles. The simulation yields a maximum diffusion coefficient of $1.44*10^{-10}$ m^2/s for the NPT ensemble.

| KEYWORDS

Molecular Dynamics; Polymers; Drug formulation; Solubility

| ARTICLE INFORMATION

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1. Introduction

The rate of adsorption and/or diffusion of active pharmaceutical ingredients (API) is influenced by the solubility and molecular weight of the drug, among other things. Most available APIs exhibit low bioavailability due to low aqueous solubility [Ting et al. 2015]. Drug-polymer formulations are therefore employed to improve the bioavailability of insoluble drugs to increase their oral absorption.

In recent times, polymer-drug miscibility has been predicted by molecular dynamics (MD) simulations with respect to the so-called Hildebrand solubility parameter [Pyrhönen, 2021; DeBoyace, 2018]. Takhulee et al. (2017) used MD simulation to investigate the miscibility of polylactide-polyethylene glycol (PLA-PEG) blends with different PEG mole fractions using the Flory-Huggins interaction (χ) parameter and found that PLA-PEG copolymer blends are miscible at low PEG concentrations and immiscible when PEG content is > 50 wt%. Pyrhönen et al. (2021) recently predicted favorable interactions between poly (decalactone) (PDL) and seven different hydrophobic drugs using the Hildebrand solubility parameter calculated from MD simulation. The MD simulation results were confirmed using experimental validations by formulating copolymers of PDL-PEG surfactants and the drugs to achieve favorable stability at lower surfactant concentrations. Rapoport et al. (2015) reported a simple 1-D continuum model that allowed discriminating between various kinetics of released drug internalization in tumor cells. The same authors [Gupta et al. 2015] reported that variations of PEG-PDLA copolymers showed advantages in preventing drug resistance by exhibiting better performance in allowing an adequate rate of drug release via drug diffusion and/or copolymer biodegradation.

In this work, the formulation development of poorly soluble API, paracetamol, is investigated with the Hildebrand solubility parameter via MD simulations, and the effect of copolymer (PEG-PLA) chain flexibility on the API formulation is examined.

2. Materials and Method

2.1 Modelling and Characterization of polymers

The PEG model was built with the polymer builder tool of Schrödinger's Material Science (SMS) suite release 2021-1 (Schrödinger, LLC, New York, NY, 2020). PEG was modelled as a homopolymer with 10 monomers via polymerization of EG monomer with methyl group as the initiator and terminator. The polymer consists of 88 atoms with a molecular weight of 630.6 g/mol. The OPLS4 force field was implemented. Copolymers of polylactide (PLA) and PEG (PLA-PEG) (**Fig. 1**) were modelled by the random copolymerization of lactic acid and EG monomers. The copolymers contain 10 monomers, each of both PLA and PEG. (The number of monomer units was kept low to reduce simulation time). The molecular concentration ratios were achieved by adding 10 monomer chains of PLA of various concentrations. Raman spectroscopy of the monomers was carried out via the calculation of single point energy in Jaguar (Desmond), and the results are shown in **Figs. 2**. Yuniarto et al. (2016) assigned the OH group appearing at 3446 cm^{-1}, C-O-C and CH groups appearing at about 1090 cm^{-1}, and 1270 to 1360 cm^{-1}, respectively, to PEG. From **Fig. 2**., the observed peaks of the simulated IR/Raman diagrams of pure PEG and PLA are comparable to that obtained in experimental IR/Raman diagrams [Yuniarto, 2016; Caccamo, 2016], showing the near accuracy of our MD simulation.

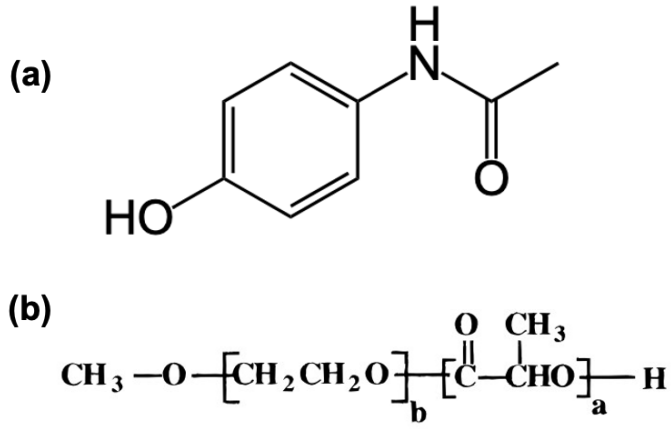

Fig. 1: Structure of (a) Paracetamol (b) PLA-PEG copolymer.

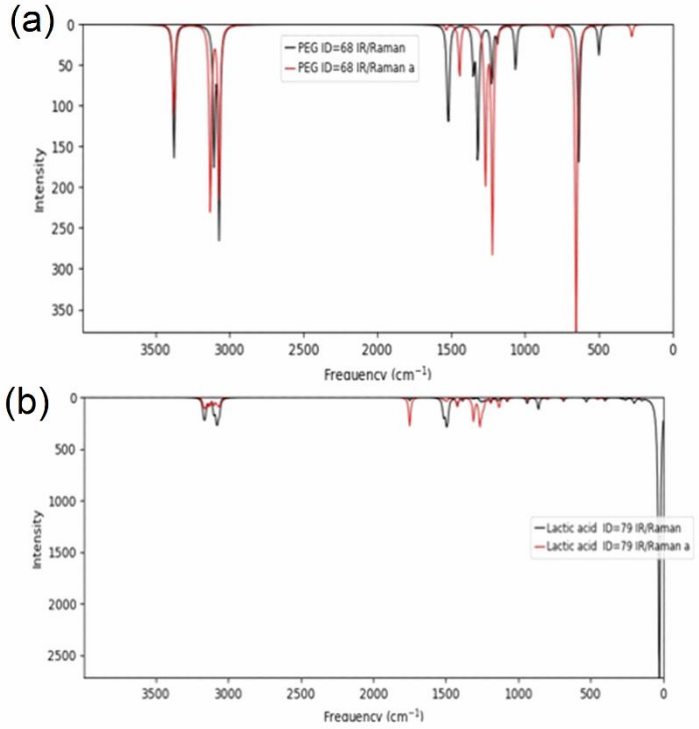

Fig. 2: Simulated IR/Raman spectra of (a) PEG and (b) PLA

2.2 Molecular Dynamics Simulations

PEG-PLA-API formulations were built using the disordered system builder tool of the SMS suite. 10 monomers were used to build a homopolymer PEG with an initial density of 0.5 g/cm^3. The initially disordered system was set to a "snapped to grid" using the OPLS4 force field with minimization. The MD simulation run was conducted for the API, polymers, and the copolymer for a total of 1.2 ns via the OPLS4 force field in "Desmond" of the SMS suite. The multistage workflow comprises a 3-stage material relaxation protocol followed by the MD and analysis. The material relaxation protocol included 100 ps of Brownian minimization. MD simulation was carried out at 300K and 1bar for 1.2 ns at 4.8 ps and 250 approximate number of frames with NPT ensemble under anisotropic coupling and a 2-fs time step. The production simulation was then performed at 300 K, and 1 bar with the Nose-Hoover thermostat and a cut off radius for short interactions at 9.0 Å. MD trajectory analysis was used to compute some bulk properties such as the cohesive energy density (CED) and the heat of vaporization (ΔH_v). The ΔH_v (kcal/mol) and Hildebrand solubility parameter (δ) are closely related according to Eq. (1) [Pyrhönen et al. 2021];

$$\delta = [(\Delta H_v - RT)/V_m]^{\frac{1}{2}} \quad (1)$$

where V_m is the molar volume. RT is the ideal gas PV term. The ΔH_v can be obtained from Eq. (2);

$$\Delta H_v = \left|E_{cell} - \sum_{i=1}^{N} E_i\right| + RT. \quad (2)$$

Where E_{cell} = the energy of periodic unit cell averaged over the MD trajectory and N = individual molecules.

The δ is also related to the CED according to Eq. (3)

$$\delta = \sqrt{CED} \quad (3)$$

Finally, the difference in solubility, the Hildebrand distance (HD), is computed as;

$$HD = \delta_1 - \delta_2 . \quad (4)$$

where δ_1 and δ_2 are the solubility parameters of the polymer and the API, respectively.

3. Results and Discussions

3.1 Miscibility of Drug-Polymer Formulation

The calculated bulk properties of the polymer, copolymers, and the API are shown in **Table 1**. The Hildebrand solubility indicates the degree of miscibility, and substances with similar δ values are more likely to be miscible. It can be seen that the copolymer blends are likely to be miscible since their δ falls within 19.63-22.13 MPa$^{1/2}$. The API has δ = 30.17 MPa$^{1/2}$ which is a little higher than that of the (co)-polymers. Further, substances with DH of < 7.0 MPa$^{1/2}$ show complete miscibility, while a value above > 10 MPa$^{1/2}$ indicates a lack of miscibility [Takhulee et al. 2017]. The average δ and HDs are shown in **Fig. 3**. An increase in the solubility of the (co)polymer decreases the HD, with low HD values indicating a higher likelihood of miscibility and high values suggesting immiscibility. From these results, the order of the API's miscibility in the polymer is PEG-PLA 0.2:0.8 > PEG-PLA 0.6:0.4 > PEG-PLA 0.8 0.2 > PEG-PLA 0.4:0.6 > PEG. This shows that PCM is poorly soluble in PEG; however, a copolymer formulation of PEG-PLA 0.2:0.8 is likely to improve the API solubility. The equimolar copolymer formulation presents the least miscibility with APIs with a HD of 10.54 MPa$^{1/2,}$ while PEG-PLA (0.2:0.8) is highly miscible with APIs. The observed high solubility of PEG-PLA (0.2:0.8) is in line with the report of Takhulee et al. (2017); i.e., PLA-PEG blends are miscible at low PEG concentrations but become apparently immiscible at higher PEG concentrations. What this means is that copolymerization increases the hydrophilicity of the polymer resulting in an increase in the solubility of the resulting copolymer. This is likely attributable to the CED and ΔH_v of the copolymer, both of which increase with the increase in the mole fraction of the PLA, resulting in stronger intermolecular forces (**Fig. 4**). The relation between vaporization and intermolecular forces of the polymer directly translates to a correlation between vaporization and solubility behavior as the same intermolecular attractive forces must be overcome to vaporize a substance as to dissolve it.

Table 1. Bulk properties of API and Polymers obtained from MD simulation

Polymer/API	Monomer Conc.	CED [kcalmol^{-1}]	ΔH_v [kcal mol^{-1}]	δ [MPa$^{1/2}$]	HD [MPa$^{1/2}$]	Specific Heat [Jg^{-1} K^{-1}]
PCM	N/A	27.56	28.16	30.17	N/A	2.96
PEG: PLA	1.0	57.32	57.91	19.92	10.25	138.0
	0.8:0.2	63.71	64.31	20.48	9.69	140.9
	0.6:0.4	67.98	65.58	21.69	8.48	218.2
	0.5:0.5	67.78	68.37	19.63	10.54	107.8
	0.4:0.6	71.32	71.91	20.36	9.81	196.6
	0.2:0.8	79.01	79.6	22.13	8.04	202.6

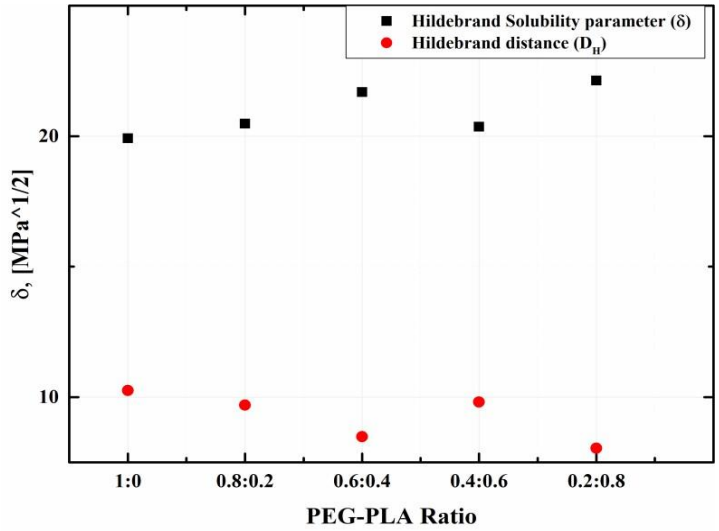

Fig. 3: Average Solubility parameter and Hildebrand distance for polymers.

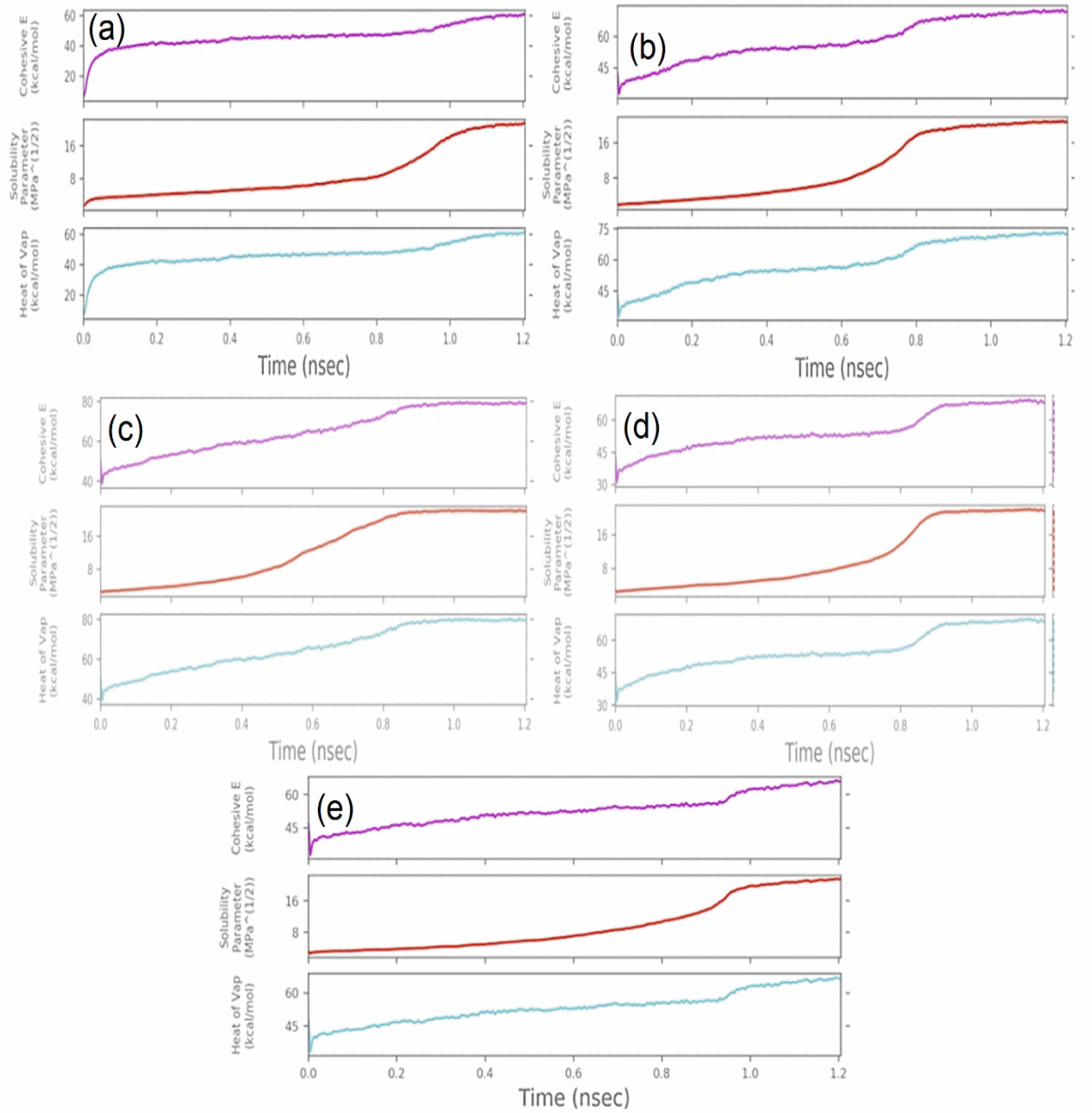

Fig. 4: Heat of vaporization (green color), solubility parameter (red color) and cohesive energy density (purple color) for all polymers studied (a) PEG (b) PEG-PLA (0.4:0.6) (c) PEG-PLA (0.2:0.8) (d) PEG-PLA (0.6:0.4) (e) PEG-PLA (0.8:0.2).

3.2 Effect of Copolymer Chain on Solubility

Polymer chain analysis was performed for all polymers using the MD simulation trajectory using properties such as persistence length (P_L), end to end distance, extended chain length, and radius of gyration (R_G) [2]. The end-to-end distance was computed for each chain in each trajectory frame, and the values were averaged over the entire trajectory. The P_L is the length at which two points on a polymer chain become decorrelated. It is a useful parameter in determining the extent of flexibility of a polymer. The R_G indicates the compactness of the shape of a polymer. A small R_G value indicates a highly compact polymer shape. **Fig. 5** shows that both P_L and R_G of PEG-PLA blend after 1.2-ns MD simulation decrease with copolymerization. A decrease in both of these parameters indicates an increase in flexibility of the copolymer chain, as can be observed in **Fig. 6**, where **the** equimolar PEG-PLA blend is highly flexible in the simulation box. Thus, it can be concluded that an increase in chain flexibility improves the miscibility of the drug-polymer formulation.

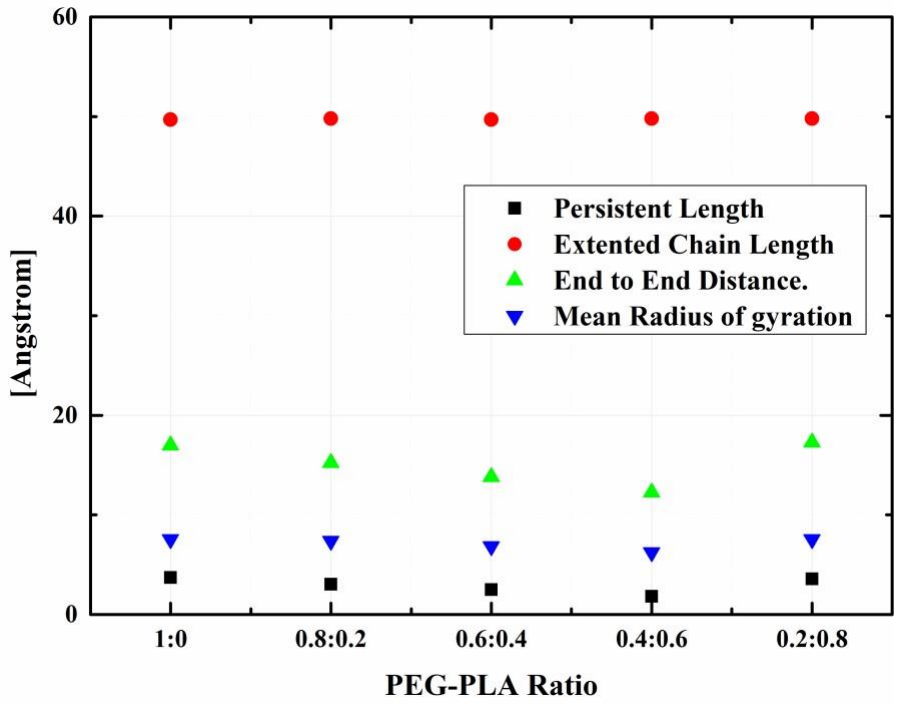

Fig 5: Average values of persistent length, end to end distance, and radius of gyration for polymers.

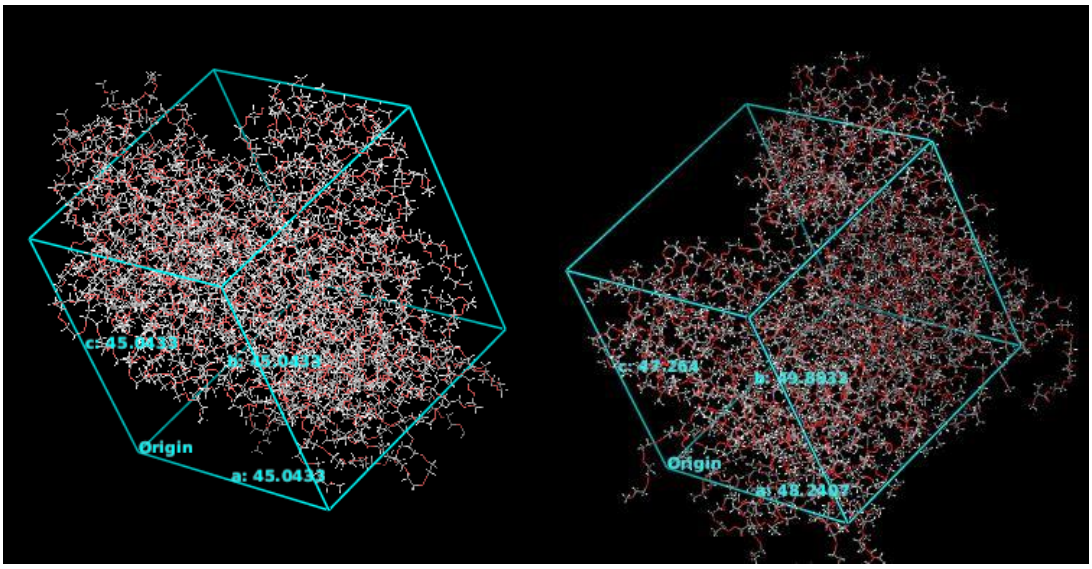

Fig. 6: Chain flexibility of PEG (left) and equimolar PEG-PLA (right) polymers

3.3 Effect of Water on API-Copolymer Interaction

Additional MD simulations were performed in the presence of water molecules. In this simulation, 20% w/w water, 10% w/w PCM, and 50% w/w PEG were used. The mobility of the drug molecules was determined by calculating the diffusion coefficient, D, via the root mean square fluctuation for the Water-PEG-API model system under different ensembles using the trajectory generated from the MD simulation at 300K and 1.0 ns simulation time. The diffusion profiles of the drug under three (3) different ensembles are shown in **Fig. 7**. The diffusion coefficient of the drug is $1.95*10^{-11}$ m^2/s in the NVT ensemble,$1.44*10^{-10}$ m^2/s in the NPT ensemble, and $1.03*10^{-10}$ m^2/s in NVE ensemble. Thus, the mobility of the API is found to be highest under the NPT ensemble with a diffusion coefficient of $1.44*10^{-10}$ m^2/s.

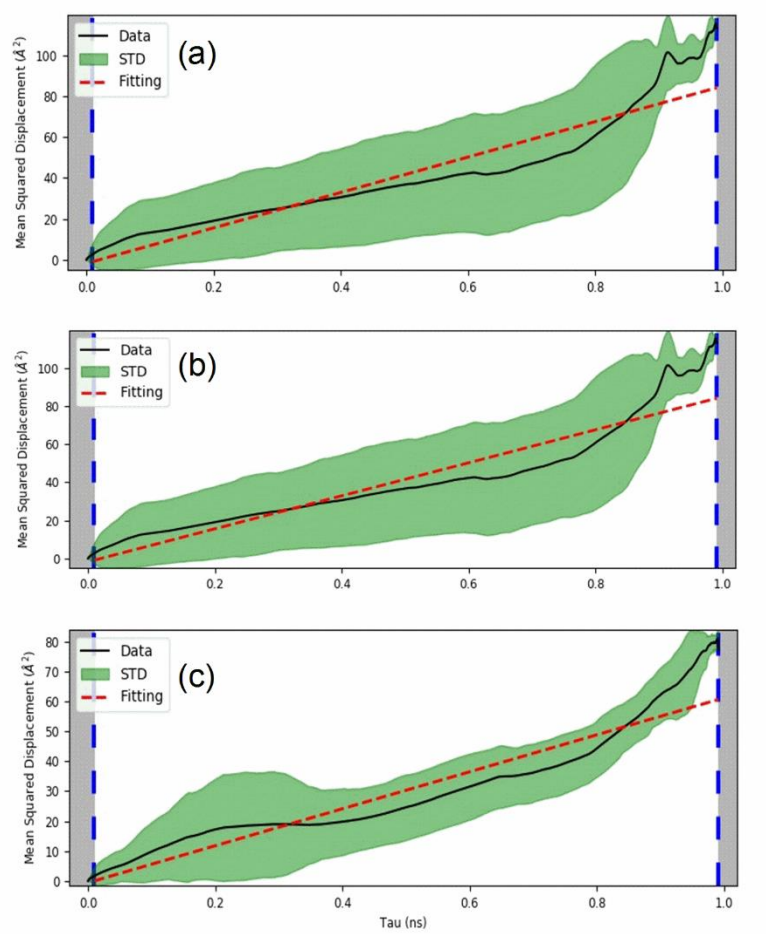

Fig. 8: Diffusion profile of the API in (a) NPT (b) NVT (c) NVE ensemble

4. Conclusions

In this study, MD simulations were employed to investigate the solubility of drug polymer formulations using the Hildebrand solubility parameter. Analysis of the solubility parameter of potential PCM-PEG-PLA formulation revealed that copolymerization of PEG with PLA improves the drug-polymer miscibility. Polymer chain analysis of various mole fractions of PEG and PLA monomers indicates that an increase in the concentration of the latter (and subsequent decrease in the concentration of the former) increases the solubility of copolymers, with higher chain flexibility. The copolymerization of PEG increased the chain flexibility of the copolymers and the miscibility of the drug-copolymer formulation by enhancing the solubility of the copolymers. The mobility of the API in PEG was found to be highest under the NPT ensemble with a diffusion coefficient of $1.44*10^{-10}$ m^2/s.

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