Molecular Simulation on the Interaction of Ethinylestradiol (EE2) with Polymer Membranes in Wastewater Purification

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ABSTRACT

Molecular dynamics (MD) simulations are performed to study the adsorption of solute organic molecules (Ethinylestradiol (EE2) and testosterone) with different polymer membranes such as polyether sulfone (PES), polyvinylidene fluoride (PVDF). The equilibrium MD simulations results for the membrane solution interface system show that the interaction of EE2 with PES is specific and strong, whereas the interaction is weak and non-specific for PVDF. The binding free energies, the non-bonded short range interaction energies and mobility are also consistent with the interaction behavior found in experiments. The adsorption of testosterone onto PES and PVDF is considered as control system. The result shows that binding free energies of PES and PVDF interacting with organic solute are consistent with experimental result in the order as; PES-EE2 > PES-Testosterone > PVDF-EE2 > PVDF-Testosterone. The formation hydrogen bonds and π-π interactions are observed between the EE2 and PES. In addition adsorption of EE2 onto polyamide 6-12 (PA612) and polystyrene (PS) membranes are predicted. This simulation study provides molecular insights on the experimental observations and helps as a computational methodology to screen the membrane materials for EE2 removal from wastewater.

Keywords

Endocrine disrupting compound; adsorption; non-equilibrium MD simulations; screening polymer membranes; water purification.

1. Introduction

The presence of endocrine disrupting compounds (EDCs) in the aquatic environments, which are exogenous chemicals responsible for adverse health effects in the intact organism [1], and have a significant impact on the mechanism and the function of the endocrine system on human health and wildlife, e.g., fishes, mammals, birds, reptiles, amphibians, and invertebrates [2, 3, 4, 5]. EDCs may be responsible for (i) reducing the effect of endogenous hormones; (ii) perturbing the synthesis and metabolism of endogenous hormones; (iii) perturbing the synthesis of hormone receptors [6, 7, 8, 9, 10]. EDCs include a wide range of molecules namely, chlorinated pesticides, herbicides, phthalates, alkylphenols, steroid hormones, including. Natural and synthetic estrogens such as estrone (E1), 17β-estradiol (E2), estriol (E3) and the synthetic hormone 17α-ethinyl estradiol (EE2) as well as progesterone, and testosterone are abundant in surface water sources [11]. EE2 is an anthropogenic substance used in human oral contraceptives and hormone therapy replacement such as osteoporosis, menstrual disorders, and prostate cancer in low ng L^{-1} range[12, 13]. The US Food and Drug administration (FDA), and the National Center for Toxicological Research published a report which classified EE2 as a major prominent estrogenic chemical in EDCs [14, 15]. The European Commission's Joint Research Centre in 2015 also listed EE2 in the watch list as a major potentially polluting compound in the aquatic environment [16]. The principal source of EE2 in aquatic ecosystem is due to the incomplete removal of EE2 in wastewater treatment [17, 18, 19, 20, 21].

Different separation techniques have been proposed and implemented for the removal of micropollutants from wastewater treatment including physical processes, biological processes and advanced oxidation processes (AOP). The physical processes can be categorized into two groups, sorption, and membrane technology such as Microfiltration (MF), Ultrafiltration (UF),

Nano filtration (NF), and reverse osmosis (RO) [22, 23, 24]. The retention of estrogen and other micropollutants in membrane based physical processes depends mainly on the type of membrane, the solution chemistry, the characteristic of the substance to be removed, and the interaction between the substance to be removed and the membrane. Different research groups have investigated various type of polymer material, which can be used efficiently in physical processes separation techniques for the removal of estrogen and micropollutants by taking into consideration the aforementioned features along with the cost effectiveness of the polymer materials. Schäfer et al., [23] presented in a review paper a non-exhaustive list of different polymer type used in adsorption studies for the removal of estrogen and other micropollutants such as polysulphone, polyester, polyamide, PES, PVDF, PS, polypropylene, cellulose and others. PES membranes have been widely used in environmental and life sciences research because of its low specific protein-binding adsorption properties, and are recommended for filtering biological and pharmaceutical solutions and have a high adsorption capacity for low-polarity organic solvents. Ng et al., [25] observed that the hydrophilic PES membrane filter has high efficiency to retain aromatic hormones especially EE2.

Many studies carried out across different countries reveal that presence of EE2 in influents and in effluents of the wastewater treatment process and receiving waters [17, 26, 27, 28], with the values from 0.2 to 1.5 ng/L (0.88 – 6.58 pM) using identical surface water. Despite the fact that some studies are able to detect the presence of EE2 in surface water in low concentrations (ng L^{-1}) [29], in many cases EE2 is not detected due to the poor limit of detection (LOD) of 1 ng/L (4.39 pM) and low concentration of EE2 which is still constitute a risk for human and wildlife [30, 31, 32, 33]. Among the studies which are able to remove EE2, only few provided insight information on the interaction mechanism between polymeric membrane and EE2 [34].

Bhandari, R.K et al., [5] presented a non-exhaustive table of estrogenic chemical occurrence in surface water from different countries. The challenge of removing EE2 from water is not only due the small concentration in which its occur and its physiological activity at such low levels, but also is small size (molecular weight of 296 g/mol) [23]. Membrane technology has been widely used, and has a lot of application in water treatment and purification due its low cost and reliable performance [35, 36]. Strong interaction with the membrane can enhance the removal of contaminants from source water.

In this paper, we present a novel and efficient molecular dynamics simulation framework to detail the removal of EE2 from aqueous solution using polymer membranes and provide molecular level information on polymer-membrane interactions with EE2. Molecular systems of EE2 interacting with two types of polymer membranes such as polyether sulfone (PES) and polyvinylidene fluoride (PVDF). The choice of PES and PVDF polymer membranes in this work is mainly to provide molecular insights to our recent experimental observations on the adsorption of EE2 [37], In addition the adsorption mechanism of EE2 onto PA612 and PS are considered. To test the concept, the systems of testosterone interacting with PES and PVDF are also included. The choices of tested polymeric membrane in this study are based on experiment result conducted to analyze the sorption between organic solute molecule and polymeric membrane [23, 25, 34, 38, 39, 40]. In section 2, atomic models and simulation system details particularly, membrane-solution interface system and solution inside the membrane are described. In section 3, results for membrane-solution interface system are presented first. Specifically, potential of mean forces (PMFs) of organic solute molecule crossing the membrane from solution phase are calculated. To further understand the interaction mechanism of the adsorption of organic solute molecule, the diffusion coefficients, the interaction energies, the hydrogen bond interactions and

π-π interactions are analyzed from the equilibrium and non-equilibrium MD simulations of solution inside the membrane system. The key observations are concluded in section 4.

2. Modeling and simulations

2.1 Atomistic Models

Figure 1 illustrates the structures of polymers, namely, PES, PVDF, PA612, and PS and solute organic molecules, EE2 and testosterone, considered in this study. The atomistic models of the polymer membrane were constructed by the Amorphous Cell module in Materials Studio software [41]. Each membrane is composed of two polymer chains with the degree of polymerization of 30, in a three dimensional periodic cell. The molecular weight (MW) of the repeat unit and density of the dry polymer for PES, PVDF, PA612 and PS are 232.26 g/mol : 1.37 g/cm^3, 64.03 g/mol : 1.78 g/cm^3, 310.48 g/mol : 1.14 g/cm^3 and 104.1 g/mol : 1.05 g/cm^3 respectively. The atomistic models of solute organic molecules, EE2 (MW-296.41 g/mol) and testosterone (MW-288.42 g/mol) were also constructed using Materials Studio. The initial structures were optimized by Density Function Theory (DFT) calculations using the Dmol^3 module. The atomic charges were assigned using Mulliken population analysis using the gradient-corrected functional algorithm (GGA) and PW91[42] with the DNP basis set. The annealing procedure was performed to equilibrate the initial structures of the polymer chain in order to correct any unstable conformations and prevent the structure from being trapped in various local minima [43, 44]. The annealing simulation was performed from the initial temperature of 300 K to the maximum of 500 K heating up every 50 K, and heating down every 50 K using NPT ensemble. The annealing procedure was cycled five times. [Figure 1 near here]

2.2 Molecular Dynamics Simulations

All molecular dynamics simulation (MD) were conducted with GROMACS 4.6.5 package [45] using OPLS force field [46]. The *topolbuild* tool was used to generate topology files (http://www.gromacs.org/Downloads/User_contributions/Other_software). The temperature and pressure was maintained at 300 K using the Parrinello-Donadio-Bussi V-rescale thermostat [47] and a pressure of 1 bar using the Berendsen barostat [48]. The short-range non-bonded interactions were modeled using Lennard Jones potentials. The long-range electrostatic interactions were calculated using the particle mesh Ewald (PME) algorithm [49, 50]. The LINCS algorithm[51] was used to constrain all bond lengths. Then the velocities were assigned according to the Maxwell-Boltzman distribution at 300 K.

2.2.1 Membrane-Solution Interface Simulation System

To calculate the relative affinity of organic solute molecules with polymeric membranes, a membrane-solution interface simulation system was constructed as shown in Figure 2 and used to compute the free energies of organic solutes crossing the polymer chain membrane from aqueous solution. The umbrella sampling method [52, 53] was used to calculated the potential mean force (PMFs), which represents the free energy change ΔG of organic solute crossing polymer chain membrane as a function of the reaction coordinate ξ, situated in the z-axis between the organic solute center of mass (COM) and the center of the polymer chain. [Figure 2 near here]

Two polymers chain and one organic solute molecules (EE2 or testosterone) were placed in a rectangular box with periodic boundary condition in three directions and solvated in water [54]. For each steered molecular dynamics (SMD) simulation pulling structures, COM of EE2 and testosterone were pulled to cross polymers membrane along the z-axis while the position

restraint was applied on the polymers chain. The SMD pulling simulations allow the organic solute molecules to sample a range of conformations at different interacting distances. The snapshots obtained from SMD pulls were considered to be the initial conformations for a series of umbrella sampling simulations. The simulation time for each window was set to 10 ns. The weighted histogram analysis method (WHAM) [55] was used to compute the free energy profiles from the umbrella sampling trajectories. In order to have an accurate binding free energy profile, 22 independent trajectories were considered for each system and used to calculate the mean binding free energies and standard error. The free energy difference ΔG between the lowest free energy in a profile at close contact and the value of the plateau at large distances apart represents the binding free energy.

2.2.2 Solution inside the Membrane

To mimic the solution environment inside the polymer, a system consisting of two chains of polymer with each of 30 repeat units, two solute organic molecules (EE2 or testosterone) and ~ 20 wt % (weight percent) water molecules was built initially using the Amorphous Cell construction module in Materials Studio software. All the systems were prepared using the same values for the contents in the simulation box. As the weight of the polymers are in the order PA612 > PES > PS > PVDF, the number of water molecules added to the system were different corresponding to the same wt %. The energy minimization was performed to relax the structures using a steep descent algorithm followed by a NPT simulation for the equilibration. After the NPT equilibration of these systems, density of the polymer matrix decreased from the dry density due to the change in its volume by swelling. To assure the simulation box was fully solvated, single point charge (SPC) [54] water molecules were added using the "genbox" tool of the Gromacs software. The Composition of polymer chains and solute molecules in the system,

as well as simulation conditions are listed in Table 1. Periodic boundary conditions were applied to the system in all three directions. The six optimized membrane cells with organic solute molecules and water molecules (the final total number of in the order, PVDF < PS < <PES<PA612) are shown in Figure 3. [Figure 3 near here]

The non-equilibrium MD simulation was conducted in order to investigate the solute organic mobility in the presence of different polymer membrane. NPT dynamics was first computed to adjust the density of the system. Furthermore, 100 ns non-equilibrium NVT simulation with an integration time step of 1 fs was performed with an acceleration of 0.1 nm ps^{-2} in *y*-direction, on the solute organic molecule and water molecule while the position restraint was applied on the polymer on backbone atoms in order to mimic the polymer chain's influence on the solute organic molecule's mobility. The diffusion process was calculated from the slope of the mean-squared displacement (MSD) of the organic solute molecule as a function of time, using the Einstein relation.

$$D_i = \frac{1}{6}\lim_{t\to\infty}\frac{d}{dt}\sum_{i=1}^{N}\left\langle\left|\vec{r}_i(\mathrm{t})-\vec{r}_i(0)\right|^2\right\rangle \quad (1)$$

where D_i is the diffusion coefficient of EE2 or testosterone, $\vec{r}_i(0)$ is its initial position vector, $\vec{r}_i(\mathrm{t})$ is its vector position at time *t*, and $\left\langle\left|\vec{r}_i(\mathrm{t})-\vec{r}_i(0)\right|^2\right\rangle$ represents the MSD of EE2 or testosterone. [Table 1 near here]

In addition, 100 ns equilibrium NVT MD simulations were conducted, from which last 50 ns trajectories were used to calculate the short-range interaction energy ($E_{\mathrm{Int}eraction}$) between the polymeric membrane and the organic solute molecule as follow,

$$E_{\mathrm{Int}eraction} = E_{Electrostatic} + E_{vdw} \quad (2)$$

where $E_{Electrostatic}$ is the electrostatic interaction energy and E_{vdw} is the van der Waals interaction energy.

The hydrogen bond (HB) between polymeric chain and organic solute molecule was computed with a sampling interval of 1 ps. The HB autocorrelation and lifetime distribution were calculated via the integration of this function [56, 57],

$$\tau_1 = \int_0^\infty C(t)\,dt \tag{3}$$

where τ_1 is the overall HB lifetime and *C(t)* is the autocorrelation function.

3. Results and discussion

3.1 Adsorption of EE2 onto polymer membrane

In order to study the adsorption phenomenon of EE2 molecule into the polymeric membrane, we first analyzed the moving of EE2 from solution to the different membrane interface in separate equilibrium MD simulations of 100 ns. Initially, EE2 molecules were placed in the solution compartment. After the system reaches the equilibrium, EE2 molecules are observed to be near the membrane surface as illustrated in Figure 4 for PES membrane and Figure 5 for PVDF membrane, respectively. This indicates the existence of an interaction between EE2 and the membrane. Figure 4 (b) and 5(b) show the corresponding number density profile of EE2 at 100 ns. The density profile was computed by dividing the simulation box into small slices in the x-direction with Δx = 0.7 nm and 0.5 nm for PES and PVDF, respectively and estimated the number densities per nm^3 for each slice. From the simulation trajectory the PES-EE2 system, it was determined that the position of EE2 molecules after the equilibration is same to the position

at t = 100 ns indicating the strong interaction at the specific position through the simulation time. On the other hand, for PVDF-EE2, we observed that EE2 molecules near the membrane interface after equilibrium, which is similar to the observation at t = 100 ns. However, the position of EE2 is not same through the simulation time indicating a weak interaction between PVDF and EE2. [Figure 4 and 5 near here]

3.2 Binding free energy

The binding free energy calculation was conducted to analyze the strength of the interaction between the small molecules, EE2 or testosterone, with polymer membranes. SMD simulation was performed and the free energy costs of the solute molecule for moving from the solution to the membrane was analyzed by computing the PMFs. The PMFs were computed from a set of umbrella sampling simulations for PES-EE2, PES-testosterone, PVDF-EE2, PVDF-testosterone, PA612-EE2 and PS-EE2 with the reaction coordinates as distance between them. This is shown in Figures 6 and 7. The free energy difference was estimated as,

$$\Delta G = G_{max} - G_{min} \quad (4)$$

where G_{max} is the free energy value when the PMF profile reaches a plateau region at long separating distances between the molecules and G_{min} is the minimum value on the PMF curve. The difference between these two free energies corresponds to the ΔG, which is the binding for polymer and organic solute molecules in this work. The values of the ΔG of binding free energies for the six complexes are listed in Table 2. It should be noted that, in the PMFs profiles the highly repulsive free energies also present at small distances. [Table 2 near here]

The highest binding free energy of organic solute molecules to the polymer corresponds to a higher interaction and *vice versa*. Among the different polymeric materials represented on Table

2, PVDF has the weakest interaction with solute molecules. The PMFs of the PVDF polymeric membrane shown in Figures 6(a) and (b) support the low interactions nature of these polymer membranes with hydrophobic and hydrophilic compounds and can be used as a control structure for adsorption [23]. The PES-EE2 binding free energy (Figure 6c) is the highest of all the tested polymeric systems, which could be the reason why PES has a strong interaction and is highly efficient to retain more EE2 compare to the other structures, as observed in our recent experiments. [25, 37]. Moreover, the simulated binding free energies are proportional to the experimental sorption data of EE2 or testosterone by these membranes. This highest binding free energy of the EE2 with PES might be due to the fact that the sulfone group R renders the polymer to polar and susceptible to forming H-bond as well as π-π interaction [23]. Furthermore the results for PES-testosterone (Figure 6d) explains the experimental observation that PES has higher efficiency to retain EE2 compared to testosterone tested in experiment [23, 25]. [Figure 6 near here]

PA612 has a polar nature and able to donate and accepts a hydrogen molecules simultaneously, which can explain the strong interaction between PA612-EE2 (Figure 7a). It should also be noted that the PA612 hydrophobicity is due to the large number of methyl sequences (-CH_2-) in PA612 repeat units [58]. Furthermore Lewis acid-base interactions and hydrophobic interactions contribute to PA612-EE2 adsorption. The PS-EE2 interaction (Figure 7b) may be due to the nature of the ring in polystyrene, which is electron neutral, when this polymer interacts with EE2, which has a benzene ring with many electrons, it could contribute to the occurrence of the π-π interaction. The hydrophobic interactions also contributes to the overall interaction between PS-EE2 [23]. [Figure 7 near here]

The binding free energies of organic solute molecule crossing the polymer membrane of all tested systems are in the order PES-EE2 > PES-testosterone > PA612-EE2 > PS-EE2> PVDF-EE2 > PVDF-testosterone.

3.3 Mean-squared displacements and diffusion coefficients

To further understand the strength of the interactions demonstrated from the binding free energies listed in Table 2 and the mobility of organic solute molecules, non-equilibrium MD simulations were carried out as described in Section 2.2.2. The mean-squared displacements (MSDs) were calculated first and the diffusion coefficients of organic solute molecules (EE2 and testosterone), in the presence of the polymer membranes, were computed based on the slope of the MSD curves in the linear range of the log-log scale Equation (1). The diffusion coefficients of organic molecules given in Table 3 show the mobility of organic solute molecule in the membrane. The position restraint was applied on the polymer to mimic the fixed polymer membrane as occurs in experiments. Figure 8a shows that the MSD of the EE2 in PVDF is higher than that of EE2 in PES, which means that interaction of EE2 with PES is stronger than interaction with PVDF and reduces the mobility. A similar trend is observed for testosterone MSD in PES and PVDF as shown in Figure 8b.

The diffusion coefficient values given in Table 3 shows that diffusion of the EE2 and testosterone organic solute in the PES membrane are less than in PVDF membrane. The lower the mobility of organic solute molecules in polymer chains means the higher binding interaction. The diffusion results show that PES has much higher interaction strength to retain EE2 compare to testosterone which is consistent with experimental results [25, 37]. Similarly, the diffusion coefficient of the EE2 and testosterone organic solute in the PVDF membrane shows that EE2

and testosterone have a high mobility in the PVDF membrane which has weaker interactions [23]. From the Table 3, it is observed that the diffusion coefficients of EE2 in the PES and PA612 polymers are smaller compared to PVDF, meaning that the mobility EE2 is reduced in the presence of the PES and PA612 polymer, which explains the high binding free energy observed in Table 2. [Table 3 near here]

A similar pattern is observed between Table 2 (binding free energy) and Table 3 (diffusion coefficients). In Figure 8c, a comparison of EE2 MSDs in the membranes PES, PS and PA612 are presented which shows that EE2 has less mobility in the presence of PES, PS and PA612. It should be mentioned that long simulation (100 ns) were performed in order to obtain accurate value of diffusion coefficients from equilibrium trajectories. However, to provide the variability of MSDs, the total 100 ns simulation was divided into two sets of 50 ns data and standard deviation errors were calculated for both MSDs and diffusion coefficients as shown in Figure 8 and Table 3 [Figure 8 near here]

3.4 Non-bonded interaction energy

The non-bonded interaction energy was computed to provide quantitative details about the interaction energies. The non-bonded (LJ and coulombic) interaction energies of solute organic molecules with polymer membrane based on short-range were calculated and listed in Table 4. The interaction energies presented in Table 4 are a similar order with PMF of PES-EE2 > PES-testosterone > PA612-EE2 > PS-EE2> PVDF-EE2 > PVDF-testosterone. This, which shows that PES-EE2 has a strong non-bonded interaction, similar with to PMFs binding free energies and the organic solute molecular diffusion coefficient. The interaction energy based on short-range interactions is not the most accurate approach for energetics analysis. However, these values

provide an overall view of energy interaction to explain the trend of the binding free energy results shown in Table 2 and the diffusion coefficients shown in Table 3, which are consistent with the experimental results [37]. [Table 4 near here]

3.5 Insight into atomistic interaction

Hydrogen bonding and the π-π interactions were analyzed to provide insight into the interaction mechanism at molecular level. Among the tested polymers, PES and PA612 are able to form strong hydrogen bonds (HB). The formation of HB for PES-EE2 can be attributed to the sulfone group R which makes the polymer polar and therefore available for H-bond with a distance of 2.9 Å as shown in Figure 9a. The lifetime of HBs was computed using Equation (2). The lifetime of HB for PES-EE2 and PES-testosterone is computed from the autocorrelation functions shown in Figure 9b and the values are 164 and 140.85 ps respectively. Figure 10a shows the numbers of HBs formed between PES-EE2 and PA612-EE2; it can be observed that PES-EE2 has more HB than PA612-EE2, which confirms the fact that PES has a much stronger interaction with the EE2 organic solute molecule, which is conformed to our experimental result [37]. [Figure 9 and 10 near here]

The PA612-EE2 HBs shown in Figure 10b have a distance of 3.0 Å and 3.2 Å and HB lifetime of 140 ps whose occurrences can be explained by the polar nature of PA612, as well as its ability to act as a hydrogen donor and acceptor [23, 34, 38]. These results explained the successful use of polyamide membrane in water treatment [34]. Furthermore, the formation of π-π interactions as well in adsorption mechanism was analyzed for PES-EE2 and PS-EE2 interactions. It has been observed the formation π-π interaction between PES-EE2 as shown in Figure 11a with a distance of 4.1 Å calculated from the two rings centroids. The observation of the formation of π-π

interaction between PES-EE2 contribute to the enhancement of the adsorption mechanism as observed in our experiment [37] and validated our hypothesis on the role of π-π interaction [37]. A similar scenario was observed for the interaction between PS-EE2 as shown in Figure 11b with a distance of 4.0 Å, calculated from the two ring centroids. [Figure 11 near here]

4. Conclusions

A comprehensive MD simulations approach to analyze the adsorption mechanism of the organic solute molecules EE2 and testosterone onto different type of polymer membranes for wastewater purification was developed. Due to the small concentration and size of EE2 (molecular weight of 296 g/mol), the removal of EE2 from wastewater is challenging. Based on the results obtained from binding free energy, diffusion coefficients, non-bonding interaction, and atomistic interaction mechanism shows that EE2 interact strongly with the PES polymer membranes. Thus, this membrane is a suitable is the removal of EE2 from wastewater. These simulation results for PES and PVDF interacting with EE2 and testosterone are consistent with the experimental findings. Our results demonstrate how different types of interaction mechanisms such as hydrogen bonds, and π-π interactions contribute to the adsorption of EE2 onto the polymer membranes. Furthermore, our computational framework has accurately predicted binding free energies for PA612 and PS polymer membranes with EE2, which explain the use, these polymer membranes in water treatment technology. The interactions between different types of polymer membranes and organic solute molecules using our computational approach and this can be used guide water purification experiments for binding interaction prediction. The proposed comprehensive screening method for the removal of micropollutants in wastewater treatment can be extended to other polymer membranes and organic solute molecules types.

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