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Prediction of drug-packaging interactions via molecular dynamics (MD) simulations

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ABSTRACT

The interaction between packaging materials and drug products is an important issue for the pharmaceutical industry, since during manufacturing, processing and storage a drug product is continuously exposed to various packaging materials. The experimental investigation of a great variety of different packaging material–drug product combinations in terms of efficacy and safety can be a costly and time-consuming task. In our work we used molecular dynamics (MD) simulations in order to evaluate the applicability of such methods to pre-screening of the packaging material-solute compatibility. The solvation free energy and the free energy of adsorption of diverse solute/solvent/solid systems were estimated. The results of our simulations agree with experimental values previously published in the literature, which indicates that the methods in question can be used to semi-quantitatively reproduce the solid-liquid interactions of the investigated systems.

1. Introduction

Drug-packaging interactions can be an issue for the pharmaceutical industry since, if pronounced, they have an impact on the safety and efficacy of drug products (Jenke, 2009). The interactions between primary packaging materials and drug products, which result from mass transport of components (and possible reaction) between the packaging material and the drug, can be divided into two phenomena: leaching and sorption. Leaching occurs when chemical components migrate out of the packaging material into the drug product. Sorption is the inverse process, i.e., when the components initially present in the drug product move into the packaging material (Jenke, 2001). Sorption can subsequently be divided into (i) adsorption during which accumulation of the drug's component occurs at the surface of the packaging material, (ii) absorption during which dispersion of the drug's component in the packaging material is observed, and (iii) permeation during which a drug formulation's component passes through the primary packaging material into the surrounding secondary packaging or the environment (Smith, 2007).

The potential adverse effects of leaching processes mainly relate to the product's safety, either directly (e.g., via the toxicity of leached substances) or indirectly (e.g., by altering the drug product's properties, such as a pH change caused by alkali ions leaching from glass). Sorption processes can directly or indirectly affect the efficacy and stability of a drug product, e.g., via the loss of an important component, such as an active pharmaceutical ingredient (API), a stabilizer or other components critical to the stability or efficacy of a drug product (Iacocca and Allgeier, 2007; Jenke, 2009).

Leaching and sorption processes are often associated with polymeric packaging materials (plastics) due to the widespread use of polymer components in drug manufacturing, processing and storage (Jenke, 2007) and to their well-documented potential to release components that may cause adverse effects (e.g., plasticizers) (Loff et al., 2000). The mobility of small molecules in polymers can be much higher than that in other packaging materials, e.g., glass, which gives rise to sorption processes (Cussler, 2009). Leaching and sorption are a potential threat to the integrity of a packaging material, causing swelling or brittleness that may result in the loss of its desired functions (Jenke, 2007).

During its lifetime a drug product repeatedly interacts with a packaging (or manufacturing) material. These interactions can be either long-term, e.g., during storage in a shipping container, or short-term, e.g., during administration via an intravenous (IV) line (Jenke et al., 2005). The latter includes, for example, parenteral drug administration, nutrition and dialysis (Loff et al., 2000). For repeated applications, such as dialysis, the amount of leached toxic components is critical due to the patients' lifetime exposure. During parenteral drug administration, API may be dispersed or absorbed into a packaging material, massively decreasing the dose that is administered to the patient and thus jeopardizing the success and effectiveness of the therapy (Treleano et al., 2009).

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Based on experimental data and heuristic assumptions, sorption and leaching can be mathematically modeled. The parameters that influence these processes include the physical and chemical natures of the drug product, the migrating component and the packaging material, as well as the migrating component's concentration, the environmental temperature and the contact time of the system (Pascall et al., 2005).

The increasing complexity of drug products (e.g., emulsions with various additives, such as stabilizers, etc.) exacerbates the analysis of the components' migration between a drug product and packaging material, rendering the successful design of drug formulations a complex optimization problem (Jenke et al., 2006).

With regard to the patients' safety, predicting the mass transport of a migrating species between two contacting phases is particularly important. In this context the main parameters that need to be examined and understood are the partition and diffusion coefficients (Piringer and Baner, 2008). Jenke et al. (2006) showed that partitioning of a migrating component between a specific packaging material and a solution in equilibrium was linearly dependent on the component's octanol/water partition coefficient ($P_{o/w}$) and on the polarity of the solution.

However, for non-equilibrium conditions, such as IV drug administration, kinetic parameters of the mass transfer are also required. Furthermore, when migration mechanisms are altered, e.g., by the presence of a cosolvent or a surfactant, polarity-based predictions may not be sufficient and additional information on the mass transfer process may be needed (Jenke, 2003). Here, experimental approaches are expensive and time consuming, and, especially, the detailed analysis of interfacial mass transport involving complex mixtures is a major challenge.

In contrast, computational models can be used to obtain more detailed and mechanistic insights into leaching and sorption processes (Hofmann et al., 2000; Piringer and Baner, 2008). Theoretically, it is possible to explicitly describe, for example, a polymer at the atomistic level exhibiting all microscopic and macroscopic properties of the true polymer (Hofmann et al., 2000; Müller-Plathe, 1994). Among the many computational methods, molecular dynamics (MD) simulations are widely used to study intermolecular interactions in the field of biochemistry and in material sciences (Hofmann et al., 2000; Lemkul and Bevan, 2010). In this work we used MD simulations to estimate two relevant material properties: (1) the solvation free energy ΔG_{solv} (Jorgensen, 1989), and (2) the free energy of adsorption. In the case of the free energy of adsorption two different methodologies were used to evaluate the applicability of such calculations towards the investigation of leaching and sorption processes: (1) direct calculations of the potentials of mean force (PMF) between a molecule in solution and a container wall (Torrie and Valleau, 1977; Valleau and Card, 1972) and (2) the linear interaction energy algorithm (LIE) (Aquist et al., 1994).

The PMF was calculated using the technique of umbrella sampling, which is frequently applied to describe molecular interactions. The resulting PMF curves emerged as a function of the interspecies distance (Lemkul and Bevan, 2010).

Two migrating components were considered in our study, the first one being 2,6-diisopropylphenol, a small-molecule API consisting of a phenol unit substituted with two isopropyl groups in ortho position to the hydroxyl group (see Fig. 1). The other migrating component was 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionic acid.

2. Methods

2,6-Diisopropylphenol was chosen as the migrating species primarily because of its clinical application as the API in anesthetic drugs, such as propofol and diprivan. It is administered via plastic syringes and IV lines (Eccleston, 2007) and may be expected to (strongly) interact with the hydrophobic environment of the polymeric packaging material due to its strong hydrophobicity (solubility in water: 150 mg/L) (Baker and Naguib, 2005). The second substance 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionic acid is an antioxidant decomposition product encountered in polyethylene materials (Jenke et al., 2006). It was considered since it is initially present in the packaging material and, in contrast to 2,6-diisopropylphenol, migrates into the solution. Furthermore, experimental data for 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionic acid are available in the literature.

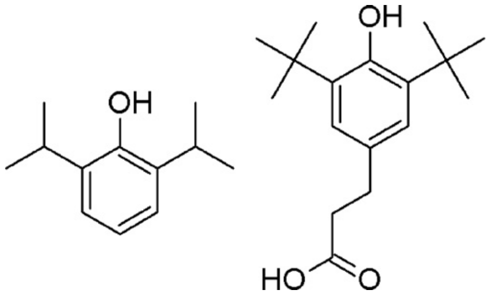

Fig. 1. Chemical structures of the investigated compounds 2,6-diisopropylphenol (left) and 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionic acid (right).

For our simulations all components were manually sketched using the AMBER11 (Case et al., 2005, 2010; Pearlman et al., 1995) module xleap. The solvents used were water, ethanol, dimethylsulfoxide (DMSO), octane and octanol. The corresponding OPLS-AA (Optimized Potentials for Liquid Simulations–All Atoms) force field (Jorgensen and Tirado-Rives, 1988) parameters (including charge) were applied to all atoms and simple point charge (SPC) water was used (van der Spoel et al., 1998). All MD simulations were performed using the GROMACS software package version 4.5.3 (Berendsen et al., 1995; Hess et al., 2008; Lindahl et al., 2001; van der Spoel et al., 2005).

For the calculation of the free energy of solvation the migrating component was put inside a cubic box with the side length of 3 nm followed by solvation with the appropriate solvent at ambient density. Periodic boundary conditions were applied and all distance-dependent properties were cut off at 1 nm. Long-range electrostatics was accounted for using particle mesh Ewald (Essmann et al., 1995). The box was equilibrated at the temperature of 300 K. The pressure of 1 bar was held constant by a Parrinello–Rahman barostat (Parrinello and Rahman, 1981) with a time constant of 0.5 ps and compressibility of $4.5 \times 10^{-6}\ \mathrm{bar}^{-1}$. 5000 steps of steepest descent minimization were followed by 100,000 steps of equilibration. The equations of motion were solved using an sd integrator (van Gunsteren and Berendsen, 1988) with a time step of 2 fs. Production runs for the calculations of free energies of solvation were performed at the following λ-values: {0.0, 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35, 0.40, 0.45, 0.50, 0.55, 0.60, 0.65, 0.70, 0.75, 0.80, 0.85, 0.90, 0.95, 1.00}. Here, λ denotes the coupling parameter describing interactions between the solute and the solvent. At $\lambda = 0$ all interactions were switched on and at the value of $\lambda = 1$ all interactions were switched off. Each run included 5 ns simulation time. The ΔG_{solv} values were calculated using the GROMACS utility *g_bar* (Bennett, 1976; Wu and Kofke, 2005).

The calculation of the LIE (Hansson et al., 1998; Su et al., 2007) is computationally less expensive than, for example, umbrella sampling because it requires only two MD simulations for each investigated system: one with the migrating component in solution and the other with the migrating component bound to the packaging material. For the LIE calculations a solute–solvent–solid

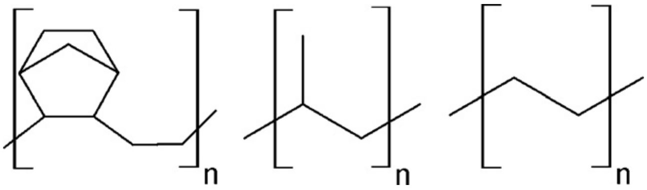

Fig. 2. Structural motives of COC, PP and PE.

simulation system was generated. The polymeric packaging material (polypropylene, cyclic olefin copolymer and polyethylene respectively) was introduced. Polypropylene (PP) and polyethylene (PE) are commonly used in packaging materials and are built from propene and ethene monomeric units, respectively, as depicted in Fig. 2. Cyclic olefin copolymers (COC) belong to a relatively new class of polymeric packaging materials (Shin et al., 2005). In our work COC made from norbornene and ethene (see Fig. 2) with the molar ratio of the monomers of 6:5 was used. Starting coordinates were generated in such a way that the polymeric chains were aligned along the *z*-axis. Via this procedure, a PP chain with a molecular weight of 15 kDa, a COC chain of 35 kDa and a PE chain of 24 kDa were generated.

To create a random packing of the polymer chain inside a simulation box, periodic boundary conditions were applied only in the *x*- and *y*-directions. In the *z*-direction walls were used to simulate a “die casting” process, where the system was compressed in the *z*-direction at the pressure of 1000 bar and the temperature of 600 K using a Berendsen barostat (Berendsen et al., 1984) and a v-rescale thermostat (Bussi et al., 2007). After equilibration for 1 ns at the elevated pressure and temperature the system was brought to ambient conditions (300 K, 1 bar) and re-equilibrated for 1 ns. A final conformation of the entangled polymer chain inside the cubic box with a side length of approximately 3 nm was produced. The final density reached was 855 kg/m^3 for PP, 910 kg/m^3 for PE and 960 kg/m^3 for COC, which was close to the real values (Lamonte and McNally, 2001; Mark, 1999). The migrating component was added to the system and randomly placed on the polymer surface. After 100 ps of equilibration the final coordinates were used as a start conformation for the solid-liquid interaction systems. The simulation setup is schematically displayed in Fig. 3.

First, the LIE between the migrating component and the packaging material was investigated. A respective solvent (water, ethanol, water/ethanol 50 vol.% and DMSO) was added to the start conformation to form a rectangular simulation system of 3 nm × 3 nm × 6 nm with periodic boundary conditions in all directions. After energy minimization and equilibration for 100 ps, a production run of 1 ns was performed. The electrostatic and van der Waals interactions in this bound state were calculated using the GROMACS utility *g_lie* with default parameters. Interactions in a free state, i.e., the migrating component in the pure solvent, were obtained from the 1 ns production run in a 3 nm × 3 nm × 3 nm box similarly to the free enthalpy of solvation calculations.

The second method used to investigate the solid-liquid interaction was an explicit calculation of the free energy of adsorption as the potential of mean force obtained from umbrella sampling calculations. The starting conformation (polymer and migrating component) was generated as described above for the LIE calculations. The box for the umbrella sampling simulations was 3 nm × 3 nm × 7 nm. The respective solvent was added and the system was equilibrated for 100 ps. Because the calculation of ΔG_{solv} and LIE values with particle mesh Ewald (PME) electrostatics would be computationally very demanding, a reaction field was employed (Tironi et al., 1995). However, for umbrella sampling calculations PME is easy to implement and more accurate than a reaction field. Thus, PME was used for the umbrella sampling calculations. As proposed by Lemkul and Bevan (2010), the Nosé–Hoover thermostat (Evans and Holian, 1983) was used along with the Parrinello–Rahman barostat (Parrinello and Rahman, 1981). To generate the starting configurations, the migrating component was pulled away from the surface for each solid-liquid combination, while the polymer was fixed with a position restraint on all heavy atoms of 1000 kJ mol^{-1}. The pulling was performed by applying a harmonic potential between the centers of mass of the polymer and the migrating component. The force constant of the potential was set at 1000 kJ mol^{-1} nm^{-2} and the reference position of the potential was changed at a rate of 0.01 nm ps^{-1} (pull rate). Each pulling simulation was conducted for 250 ps with a time step of 1 fs. Starting conformations for individual umbrella sampling windows were generated based on the resulting trajectory. The window's spacing was 0.05 nm within 0.5 nm from the surface and 0.1 nm beyond that distance (preliminary simulations showed that the PMF curve levels off towards a constant value within a distance of 1 nm from the surface). The force constant of the umbrella biasing potential was set to 10,000 kJ mol^{-1} nm^{-2} in direct vicinity to the surface and was linearly decreased to 1000 kJ mol^{-1} nm^{-2} at a distance of 1 nm from the surface. Following this procedure, twenty sampling windows were generated for each solid-liquid combination, and

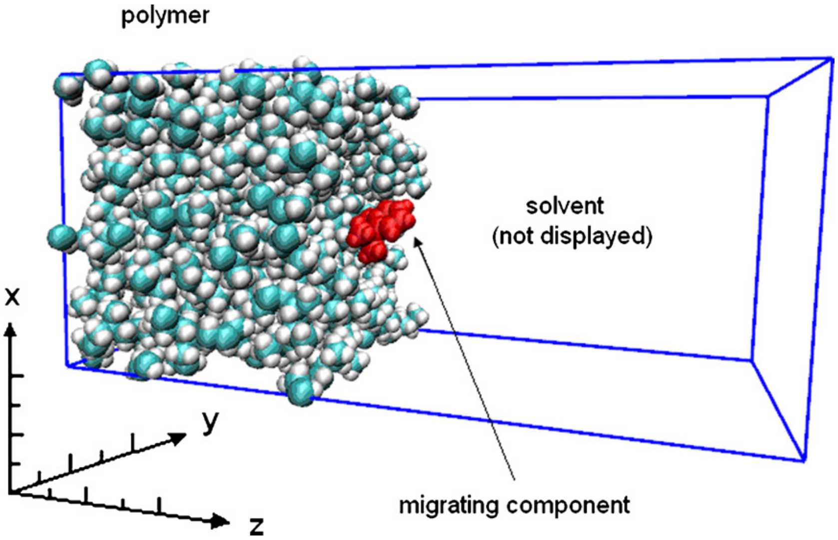

Fig. 3. Simulation setup for the LIE calculations.

Table 1
Calculated values for the solvation free energy of 2,6-diisopropylphenol in different solvents.

Solvent	ΔG_{solv} (kJ mol^{-1})
Water	−8.07 ± 0.17
Octanol	−37.11 ± 0.35

Table 2
Calculated values of the linear interaction energy for 2,6-diisopropylphenol in different environments.

Solvent	LIE values (kJ mol^{-1})		
	PP	COC	Pure solvent
Water	−36.9	−32.0	−45.5
DMSO	−41.0	−40.1	−43.3
Ethanol	−34.3	−33.2	−35.4
Octane	−18.5	−18.1	−18.4

the results were analyzed using the weighted histogram analysis method (WHAM) (Hub et al., 2010).

3. Results and discussion

3.1. Free enthalpy of solvation

The solvation free energy in two solvents is related to the partition coefficient via Eq. (1):

$$P_{o/w} = \exp\left(\frac{\Delta G_{hyd} - \Delta G_{oct}}{RT}\right) \qquad (1)$$

$P_{o/w}$ denotes the octanol water partition coefficient that is frequently used to describe the hydrophilic and hydrophobic properties of solute molecules. In this expression ΔG_{hyd} is the solvation free energy in water and ΔG_{oct} is the solvation free energy in octanol. R and T denote the gas constant and thermodynamic temperature, respectively.

The calculated values displayed in Table 1 support the assumption that the solute molecule 2,6-diisopropylphenol is highly soluble in organic solvents and less soluble in water. Furthermore, according to the calculated values, a $\log P_{o/w}$ for the solute molecule of 5.05 was obtained using Eq. (1). The experimental value for the $\log P_{o/w}$ of 2,6-diisopropylphenol found in the literature is 4.16 (Baker and Naguib, 2005). Though deviating from the experimental value, the difference between the calculated and the experimental value lies within an acceptable range. Nevertheless, the calculation of the $\log P_{o/w}$ was mainly performed to check the general validity of the chosen OPLS-AA parameters for the following more elaborative simulation setup.

3.2. Linear interaction energy

The LIE was used to calculate the binding free energy of 2,6-diisopropylphenol to the surface of the packaging material in different solvents. The obtained values are displayed in Table 2. The investigated environments were created by placing the migrating component in close vicinity to the surface of the two polymers (PP and COC) representing the “bound state” in which the migrating component was bound to the surface and adding different solvents. The LIE values for the “free state,” in which the migrating component was dissolved in a pure solvent, were calculated as well.

Interestingly, the difference in the LIE values for the bound state and the free state was only significant for the solvent “water” yielding the binding free energy ΔG_{bind} of +8.6 kJ mol^{-1} for PP and the value of +13.5 kJ mol^{-1} for COC. For all organic solvents there was no significant difference between the “bound state” and the “free state”. A possible explanation for this lack of difference in binding free energies for the systems containing organic solvents could be that the LIE algorithm failed to fully account for entropic contributions. The fact that for the solvent “water” the binding free energy is even significantly positive implies that there is no tendency of the migrating component to bind to the polymer surface. This finding does not agree with a visual analysis of the simulated trajectory. In the case of water the migrating component never leaves the polymer surface during the simulation. Moreover, test simulations in which the migrating component was placed at 1 nm distance to the polymer surface showed a tendency of the migrating component to rapidly adsorb to the surface. It is likely that, while the migrating component strongly interacts with water (an explicitly negative LIE value), it is the difference in the water-water interactions between the bound and the free state of the solvent not captured by LIE calculations, that accounts for this effect. This results in an overall poor solubility of the migrating component and the tendency to leave the hydrophilic aquatic environment and move towards the hydrophobic polymer surface.

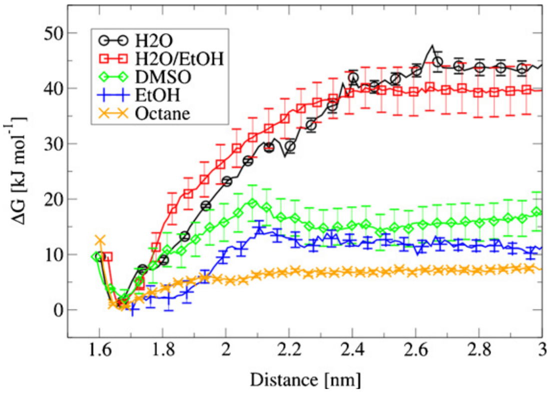

Fig. 4. Potential of mean force curves for the adsorption of 2,6-diisopropylphenol on cyclic olefin copolymer in different solvents (error estimates generated using Bayesian bootstrapping).

3.3. Umbrella sampling

The umbrella sampling simulations were used to investigate the difference in the free energy ΔG with respect to the distance of the migrating component to the polymer surface. The following figures show the calculated PMF-values for the adsorption of the migrating component 2,6-diisopropylphenol on two polymer surfaces, i.e., cyclic olefin copolymer (Fig. 4) and polypropylene (Fig. 5),

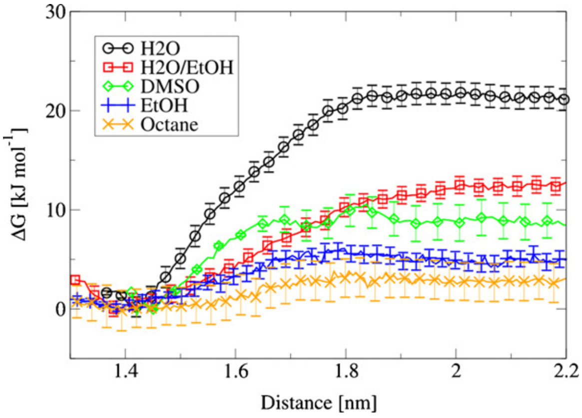

Fig. 5. Potential of mean force curves for the adsorption of 2,6-diisopropylphenol on polypropylene in different solvents (error estimates generated using Bayesian bootstrapping).

Table 3
ΔG values obtained from the PMF curves for the adsorption of 2,6-diisopropylphenol on polypropylene and cyclic olefin copolymer in different solvents.

Solvent	ΔG (kJ mol^{-1})	
	COC	PP
Water	43	21
Water/EtOH, 50:50	38	12
DMSO	16	9
Ethanol	11	5
Octane	6	3

in different solvents. The local minimum at 1.65 nm in Fig. 4 resembles the starting position. At a smaller distance the repulsion from the polymer surface leads to a drastic increase in energy. In Fig. 5 there is no sharp minimum. The energy levels off in the vicinity of the polymer surface and increases only slightly. This can probably be explained with the lower density of polypropylene compared to cyclic olefin copolymer.

The error bars generated by the GROMACS utility *g_wham* are estimated using Bayesian bootstrapping. Bootstrapping is used to estimate the uncertainty of a quantity that is calculated from a large set of observations, in this case the histograms obtained from the umbrella sampling windows. The Bayesian bootstrapping technique resamples the PMF based on an estimated probability distribution underlying the histograms, assigning random weights to them (Hub et al., 2010). Table 3 shows the obtained values for the free energy of adsorption differences between a local minimum of the curve representing the adsorbed state and the constant part of the curve where the migrating component is solely in the pure solvent.The PMF curves show that the behavior of the migrating component strongly depends on the solvent. As expected, the biggest energy difference was between the migrating component in water and the migrating component adsorbed to the hydrophobic surface. In contrast to the results of the LIE method, the ΔG value obtained from the PMF curve was negative, indicating favorable adsorption to the surface. For all solvents the ΔG value obtained from the PMF curve correlated with the solvent's polarity index, as reported in the literature. Fig. 6 shows a plot of the ΔG values versus the polarity index of the used solvent. The polarity index for 50 vol.% mixture of water and ethanol was calculated according to Eq. (2):

$$P'_{\mathrm{m}} = \varphi P'_1 + (1-\varphi)P'_2 \qquad (2)$$

where P'_{m} is the polarity index of the mixture and φ is the proportion (vol.) of the solvent 1 in the mixture (Jenke, 2001).

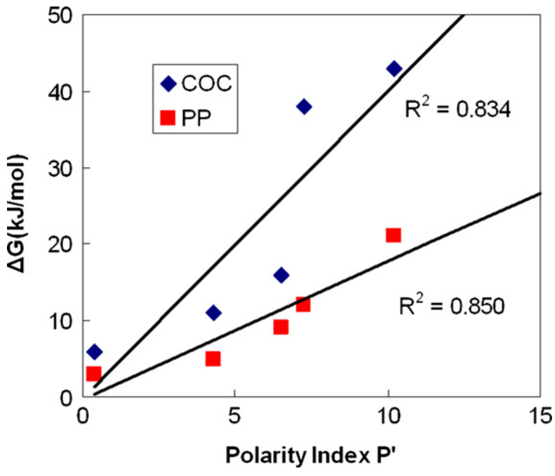

Fig. 6. Plot of the ΔG values obtained from the potential of mean force curves vs. the polarity index.

Table 4
Solvent polarity index according to Snyder (Schoenmakers, 1986; Snyder, 1974).

Solvent	P′
Water	10.2
DMSO	6.5
Ethanol	4.3
Octanol	3.4

Table 5
ΔG values obtained from the PMF curves for the adsorption of 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionic acid on polyethylene in different solvents.

Solvent	ΔG (kJ mol^{-1})
EtOH/water 0%	34
EtOH/water 15%	33
EtOH/water 30%	28
EtOH/water 45%	23
EtOH/water 100%	6.5

Table 4 shows the polarity index according to the Snyder classification of solvents (Schoenmakers, 1986; Snyder, 1974).

Evidently, the profiles of the plots in Fig. 6 are similar, although the values for COC are proportionally higher than those for PP. A linear regression through the plotted values clearly shows a correlation between the polarity index of the solvent and the corresponding ΔG value.

To demonstrate the validity of the method for binary solvent mixtures a leaching experiment published by Jenke et al. (2006) was performed as a test case. In their work Jenke et al. (2006) show that 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionic acid, leaching from a PE material accumulates in contacting solvents according to their respective polarities. A system was set up as described above and ethanol/water mixtures with an ethanol content of 15, 30 and 45 vol.% and water were used as solvents (see the resulting PMF curves in Fig. 7). Table 5 shows the obtained values for the enthalpy differences between a local minimum of the curve representing a close vicinity to the surface and the constant part of the curve where the migrating component is solely in the pure solvent.

Fig. 8 shows the linear correlation between the free energy of adsorption for the migrating component and the polarity of the used solvent and the experimentally determined values for the investigated system published by Jenke et al. (2006). The displayed concentrations represent the amount of migrating component remaining in the polymer when the polymer was brought into contact with the respective solvent.

The results indicate that the employed method can be used to predict solid-liquid interactions under the investigated conditions. The method yields semi-quantitative results for pure solvents as

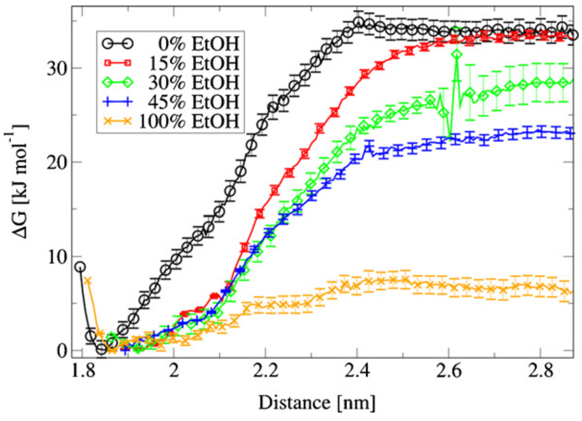

Fig. 7. Potential of mean force curves for the adsorption of 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionic acid on polyethylene in different ethanol/water mixtures.

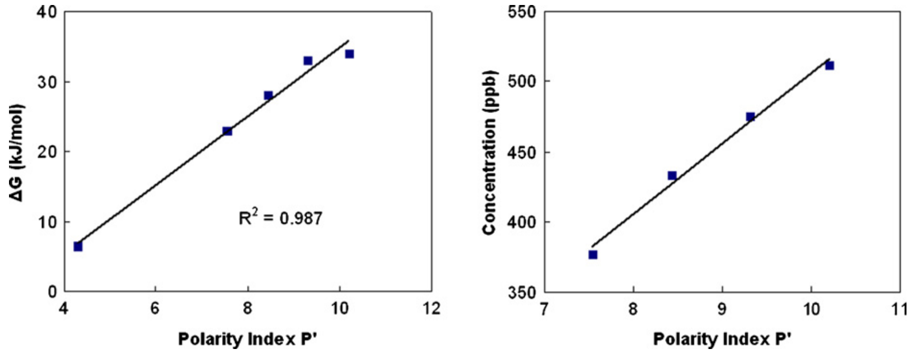

Fig. 8. Plot of the ΔG values obtained from the potential of mean force curves vs. the polarity index (left), amount of migrating component remaining in the plastic material (right).
According to Jenke et al. (2006).

well as for binary mixtures. Interestingly, although the simulations were based only on the adsorption of the migrating component to the polymer surface, the resulting free energy of adsorption values correlate with the findings from leaching experiments. In reality the migrating component is also absorbed and migrates through polymeric materials. A simulation of this behavior would computationally be much more expensive since the time and length scales of such a process are far beyond the reach of state-of-the art simulation methods. Fortunately, the free energy of adsorption, which can be obtained with a reasonable computational effort, shows relative trends that stand in accordance with experimental findings published in literature. This indicates that the adsorption is a significant part of the overall migration process and the free energy contribution that relates to further migration into/out of the polymer does not depend on the used solvent.

4. Conclusion

The solid-liquid interactions of small organic solute molecules with polymer surfaces and common solvents were investigated using MD simulations to estimate the solvation free energy and the free energy of adsorption. The results may be summarized as follows:

(1) The investigated simulation method can be used to predict the octanol/water partition coefficient based on a calculation of the solvation free energy.
(2) The calculation of the free energy of adsorption was performed in two ways. The first one, linear interaction energy algorithm (LIE), did not yield significant differences for the binding free energy between the solute and the polymer's surface for all investigated organic solvents. For water the obtained value indicated no adsorption of the solute to the surface. This does not agree with the results obtained from direct calculations of potentials of mean force between the solute and the surface.
(3) The second approach–a direct calculation of the potential of mean force between a molecule in solution and a container wall–yielded results for the free energy of adsorption that correlate well with the polarity index of the used solvent, which agrees with published experimental results.
(4) The results furthermore indicate that, generally, MD methods and, specifically, the OPLS-AA parameters used in our study can successfully be used to investigate such solid-liquid interactions for different pure solvents as well as for binary mixtures.
(5) Although only the adsorption of solute molecules on polymers was investigated in the simulations, the results correlate with the findings from leaching experiments (the migration into/out of the polymer by either the migrating component or the solvent would in principle be possible. However, due to the small timescales examined this cannot be observed). This indicates that the contributions relating to the migration into/out of the polymer do not depend on the used solvent. Further experiments to clarify this statement are necessary.
(6) Since many drug products have a rather complex composition, simple polarity-based models for the prediction of drug packaging interactions might be insufficient. A more rigorous modeling approach, that is capable of including additional parameters, e.g., cosolvents or ionic strength, such as the method described in this work, might help overcome such difficulties.

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