Investigation of Migrant–Polymer Interaction in Pharmaceutical Packaging Material Using the Linear Interaction Energy Algorithm

PETER FEENSTRA,[1] MICHAEL BRUNSTEINER,[2] JOHANNES KHINAST[1,2]

[1]Institute of Process and Particle Engineering, Graz University of Technology, Graz, Austria
[2]Research Center Pharmaceutical Engineering, Graz, Austria

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ABSTRACT: The interaction between drug products and polymeric packaging materials is an important topic in the pharmaceutical industry and often associated with high costs because of the required elaborative interaction studies. Therefore, a theoretical prediction of such interactions would be beneficial. Often, material parameters such as the octanol water partition coefficient are used to predict the partitioning of migrant molecules between a solvent and a polymeric packaging material. Here, we present the investigation of the partitioning of various migrant molecules between polymers and solvents using molecular dynamics simulations for the calculation of interaction energies. Our results show that the use of a model for the interaction between the migrant and the polymer at atomistic detail can yield significantly better results when predicting the polymer solvent partitioning than a model based on the octanol water partition coefficient. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:3197–3204, 2014

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INTRODUCTION

Polymers are ubiquitously used in the food and pharmaceutical industry as packaging materials or process aids. Therefore, during their production, shipment, and storage, the exposure of pharmaceutical products to various polymers is common.[1,2] Every such exposure bears the risk of undesired migration of compounds present in either the drug product or the polymer. Consequently, adverse safety effects cannot be excluded.[3,4] The mass transport of migrants (and possible reaction) between the polymer and the drug product are usually classified as leaching and sorption. Leaching describes the process of migration from the polymer into the drug product, whereas sorption describes the inverse process, that is, when a migrant, such as an active pharmaceutical ingredient (API), moves into the polymer.[5] Sorption is further divided into (1) adsorption (accumulation of a migrant at the surface of the polymer), (2) absorption (dispersion of a migrant in the polymer), and (3) permeation (transition of a migrant through the polymer).[6]

Especially in the pharmaceutical industry, the experimental analysis of possible adverse interactions can lead to significant costs because of the rigorous regulatory requirements and the fact that with the increasing complexity of drug products (e.g., emulsions with various additives, such as stabilizers, etc.) the analysis of the migrants' interaction between a drug product and polymers is not straightforward. A method to overcome these problems is to perform experiments not with the actual complex drug product but with a simplified (simulated) product.[4] From the corresponding experimental data, when combined with heuristic rules, mathematical models of migrant–polymer interactions can be established with the main goal of predicting the mass transport of the migrant between the drug product and the polymer. The mass transport itself can be described by two main parameters: the partition and the diffusion coefficient.[7] Partition and diffusion coefficients are determined by the physical and chemical natures of the (simulated) drug product, the migrant, and the polymer, as well as the migrant's concentration, the environmental temperature, and the contact time of the system.[8,9]

One established parameter for the prediction of migrant transport (e.g., cell membrane transition by a drug molecule) is the octanol–water partition coefficient ($P_{o/w}$).[10–12] It is defined as the ratio of the equilibrium concentrations of a specific migrant in octanol (C_o) and water (C_w) in Eq. (1). A similar property is the equilibrium interaction constant E_b that describes the ratio of the equilibrium concentrations of a migrant in the polymer (C_p) and the adjacent solvent (C_s) in Eq. (2).

$$P_{o/w} = \frac{C_o}{C_w} \tag{1}$$

$$E_b = \frac{C_p}{C_s} \tag{2}$$

According to Jenke et al.,[13] the log E_b correlates linearly with the log $P_{o/w}$ as denoted in Eq. (3) with regression constants for the individual polymer. Moreover, it also linearly correlates with the polarity of the solvent P_m as given in Eq. (4).[5,14]

$$\log E_b = a \times (\log P_{o/w}) + b \tag{3}$$

$$\log E_b \propto P_m \tag{4}$$

Ideally, these relationships should allow the prediction of the equilibrium concentration of a migrant in either the drug

Correspondence to: Johannes Khinast (Telephone: +43-316-87330400; Fax: +43-316-87330402; E-mail: khinast@tugraz.at)

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product or the polymer based on the materials' properties and the initial concentrations.

As both properties, $P_{o/w}$ and E_b, are determined by the molecular structures of and the intermolecular forces between the involved molecules, a more sophisticated investigation of the migrant's behavior should be based on microscopic or atomistic properties. Microscopic properties can be the structural parameters such as polymer chain length, chain segment angles, averaged distance between chains, migrant collision diameters, and so on, whereas sophisticated atomistic models use very elementary physical–chemical data. These methods are capable of producing remarkable results but they require powerful computers, appropriate software, and a good model parameterization.[7,15] For example, molecular dynamics (MD) simulations are widely used in the field of biochemistry and material sciences[16,17] as well as in pharmaceutical sciences.[15,18–22]

In recent studies,[23] we demonstrated the applicability of MD simulations for the investigation of leaching and sorption processes. We used different approaches to evaluate the applicability of MD simulations toward the investigation of leaching and sorption processes such as the calculation of the solvation-free energy $\Delta_{solv}G$,[24] the potentials of mean force between a molecule in solution and a container wall,[25,26] and the linear interaction energy (LIE) algorithm.[27]

Most applications of the LIE algorithm are found in the estimation of relative protein–ligand binding affinities.[28,29] It is computationally less expensive than other computational methods, such as thermodynamic integration or free energy perturbation, because it requires only two MD simulations for each investigated system: one with the migrating component in solution (free state) and the other with the migrating component bound to the polymer (bound state). More importantly, with current algorithms/methodologies, the direct application of thermodynamic integration or free energy perturbation is not possible for solid solvents, such as polyvinylchloride (PVC) at ambient conditions, whereas the application of LIE is comparatively straightforward. The electrostatic and van der Waals interactions in the free and in the bound state are computed and the binding-free energy can be estimated by a linear combination of these values.[28,30,31] Therefore, the LIE method promises to be a valuable tool for the investigation and prediction of migrant–polymer interactions in an analogy to protein–ligand interactions.

Here, we apply the LIE method for the prediction of the migration of small, drug-like molecules between a polymer and a solvent and compare the results with those predicted with a log $P_{o/w}$ to log E_b relation. The used molecules show various chemical structural motifs and diverse log $P_{o/w}$ values. The polymers used in this study were polyethylene (PE) and PVC, which are commonly used in packaging materials in the pharmaceutical industry.

METHODS

For our simulations, all components were manually sketched using the AMBER[32–34] module xleap. The corresponding OPLS-AA[35] (optimized potentials for liquid simulations—all Atoms) force field parameters (including charge) were applied to all atoms. When required, small manual adjustments were made to partial charges to ensure that the molecules net charge was zero. The topology files can be found in the Supporting Information. All MD simulations were performed using the GROMACS[36–39] software package version 4.5.3. VMD 1.8.7[40] was used to visually analyze the investigated systems.

For the calculation of the migrant–solvent interaction systems, three migrant molecules were put inside a cubic box with the side length of 4 nm followed by solvation with the solvent at ambient density. Periodic boundary conditions were applied and van der Waals interactions were cut off at 1.4 nm. Long-range electrostatics was accounted for using particle mesh Ewald.[41] The box was equilibrated at the temperature of 300 K using a Nosé–Hoover thermostat.[42] The pressure of 1 bar was held constant by a Berendsen Barostat with a time constant of 0.5 ps and compressibility of 4.5×10^{-5} bar^{-1}.[43] Five thousands steps of steepest descent minimization were followed by 100,000 steps of equilibration. The equations of motion were solved using a time step of 2 fs. Production runs for the LIE calculations spanning 1 ns of simulation time were performed for each migrant molecule–solvent pair.

Initial structures for the systems containing the migrant immersed in the packaging material were generated as follows. Starting coordinates for the polymeric packaging material (PVC and PE) were generated in such a way that the polymeric chains were aligned along the *z*-axis. Via this procedure, a PVC chain with a molecular weight of 25 kDa and a PE chain with a molecular weight of 19 kDa were generated. Then, three molecules of the migrant molecule were added to the system and randomly placed in the simulation box. Initially, 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 a pressure of 1000 bar and a temperature of 600 K. Because of the resulting large forces, a time step of 1 fs had to be used during compression to ensure stability of the system. Temperature was controlled using a Berendsen thermostat.[43] 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 to reach a final conformation of the entangled polymer chain inside the cubic box with a side length of approximately 3 nm. The final densities, 1330 kg/m^3 for PVC and 900 kg/m^3 for PE, are close to experimental values.[44] The final coordinates were used as a starting conformation for the migrant–polymer production runs, again 1 ns of simulation time for each migrant molecule–polymer pair. Interaction energies between the migrant and the polymer and between the migrant and the solvent were analyzed using the GROMACS utility *g_lie*.

This way, LIE values for the migrating component inside the two polymers (PVC and PE) representing the "bound state" were calculated. LIE values for the "free state," in which the migrating component was dissolved in a pure solvent, were calculated as well. The difference in the free energy values for the two states is then defined as ΔG_{bind} (Eq. (5)).[28]

$$\Delta G_{bind} = \alpha_{polymer}\left\langle V_{l-s}^{vdW}\right\rangle_{bound} - \alpha_{solvent}\left\langle V_{l-s}^{vdW}\right\rangle_{free} + \beta_{polymer}\left\langle V_{l-s}^{el}\right\rangle_{bound} - \beta_{solvent}\left\langle V_{l-s}^{el}\right\rangle_{free} \quad (5)$$

$\langle V\rangle$ denotes the simulation average of the nonbonded potential energy between ligand (subscript "l" in this case is the migrant molecule) and surrounding (subscript "s" is a polymer or solvent). α and β are the scaling factors for van der Waals