Drug–Polymer Interactions at Water–Crystal Interfaces and Implications for Crystallization Inhibition: Molecular Dynamics Simulations of Amphiphilic Block Copolymer Interactions with Tolazamide Crystals

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ABSTRACT: A diblock copolymer, poly(ethylene glycol)-block-poly(lactic acid) (PEG-*b*-PLA), modulates the crystal growth of tolazamide (TLZ), resulting in a crystal morphology change from needles to plates in aqueous media. To understand this crystal surface drug–polymer interaction, we conducted molecular dynamics simulations on crystal surfaces of TLZ in water containing PEG-*b*-PLA. A 130-ns simulation of the polymer in a large water box was run before initiating 50 ns simulations with each of the crystal surfaces. The simulations demonstrated differentiated drug–polymer interactions that are consistent with experimental studies. Interaction of PEG-*b*-PLA with the (001) face occurred more rapidly (≤10 ns) and strongly (total interaction energy of −121.1 kJ/mol/monomer) than that with the (010) face (~35 ns, −85.4 kJ/mol/monomer). There was little interaction with the (100) face. Hydrophobic and van der Waals (VDW) interactions were the dominant forces, accounting for more than 90% of total interaction energies. It suggests that polymers capable of forming strong hydrophobic and VDW interactions might be more effective in inhibiting crystallization of poorly water-soluble and hydrophobic drugs in aqueous media (such as gastrointestinal fluid) than those with hydrogen-bonding capacities. Such in-depth analysis and understanding facilitate the rational selection of polymers in designing supersaturation-based enabling formulations. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:2132–2141, 2015

Keywords: dissolution; crystallization; morphology; polymeric drug delivery systems; solubility; tolazamide; molecular dynamics simulation; drug–polymer interaction; hydrophobic interaction; van der Waals interaction

INTRODUCTION

Synthetic and natural polymers have been widely used in developing and manufacturing pharmaceutical products. The applications include[1,2] (but are not limited to) binding the particles of a solid dosage form, changing the flow properties of active pharmaceutical ingredient (API), masking unpleasant taste of a drug, modifying drug release characteristics, stabilizing suspensions, enabling drug delivery, and inhibiting crystallization of APIs. The ability of polymers to inhibit crystallization of drug molecules has promoted intense research in recent years. Polymers are used to stabilize metastable solid form in formulations, that is, amorphous solid dispersions (ASDs[3–5]), to deliver poorly water-soluble small molecular drugs (Class II and IV in Biopharmaceutics Classification System[6]) that represent approximately 90% of current pipeline drugs across the pharmaceutical industry.[7] Polymers are also used to maintain supersaturation during dissolution of enabling formulations for maximizing formulation performance.[8–11] Finally, polymers can play an important role in modifying the crystal habit during solution crystallization.[12–14]

Crystallization inhibition originates from drug–polymer interactions. Understanding the mechanism of how drug molecules interact with the polymer will help us to select a better polymer for formulating and delivering drug molecules. Molecular dynamics (MD) simulations can add insights that otherwise are difficult to gain by experimental methods, therefore they are well suited for this purpose. The reported use of MD simulations in drug crystallization inhibition by polymers can be divided into two main areas: drug–polymer interactions in amorphous systems that primarily deal with solubility or miscibility[15–20] and in crystal systems that address crystal growth inhibition. In the latter, there are only a few published studies in recent years. Zhu et al.[21,22] simulated the interaction of several additives (such as hydroxypropyl methylcellulose, HPMC) in water with crystal surface of fenofibrate[21] and griseofulvin.[22] A short HPMC chain (five repeating units) was constructed and placed into a small water box (1500 water molecules) with the simulation carried over a short duration (600–800 ps). The simulated binding energies between the additives and crystal surface were correlated with the experimental results when these additives were found to reduce the particle size of recrystallized griseofulvin. Yani et al.[23] reported a 400-ps MD simulation of large polymers [225 monomers for poly(vinylpyrrolidone) (PVP) and 62 for HPMC] with different crystal phases of salbutamol sulfate in vacuum (in the absence of water). Hydrogen bonding between PVP and salbutamol sulfate, which was approximately 40% of total binding energy, was thought to dominate in prohibiting crystal growth. The water-soluble polymers used in drug crystallization inhibition strongly interact with water molecules. As a result, the

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interaction with drug molecules is expected to change in the presence of water. For examples, Taylor and coworkers[24,25] reported that PVP, which is an effective crystallization inhibitor to felodipine in ASDs, at low relative humidity (RH) significantly reduced its effectiveness at high RH[24] and even lost its ability in aqueous dissolution medium.[25] The loss of effectiveness was ascribed to the strong interaction of PVP with water molecules. Apparently, more studies are needed to improve upon the MD simulation methodologies (i.e., sufficiently long simulation time under more realistic conditions) in order to demonstrate the validity and utility of MD simulation as an emerging and powerful technique for such applications. More importantly, it is necessary to conduct more careful analysis in interaction energies involved in the drug–polymer interaction for the purpose of understanding the mechanism of crystallization inhibition by polymers in aqueous solutions. The purpose of our present work, therefore, is to develop improved MD simulation methods to study the molecular level mechanism and energetics involved in crystal growth inhibition by polymers in an aqueous solution.

The model system chosen for this study comprised tolazamide (TLZ), an oral hypoglycemic agent, and poly(ethylene glycol)-block-poly(lactic acid) (PEG-*b*-PLA), an amphiphilic block copolymer based on the interesting work published by Kuldipkumar et al.[12,26,27] PEG-*b*-PLA was observed to change the TLZ crystal habit from needle to plate shape[12] (shown in Fig. 1). PEG-*b*-PLA exerts this strong habit modification at very low concentration (3–10 ppm) regardless of PEG to PLA monomer ratios in the polymer.[27] Three major faces (100), (010), and (001) were identified. For the needle crystals obtained in the absence of PEG-*b*-PLA in Figure 1, the largest face was found to be (010), whereas the smaller faces have indices (100) (tip of the needle) and (001) (side face), respectively. Crystals of TLZ obtained in the presence of the PEG-*b*-PLA became plate-like. The largest plate face (the dominant face) was determined to be (001). The smaller faces are the (100) (side of the plate), the (010) (tip of the plate), and the (1–11) (the face that cuts the side and tip), respectively.[27] Because any faces that grow slowly will appear in the final crystal as the dominant large faces, it is clear that PEG-*b*-PLA has selectively interacted with (001) phase of TLZ crystal to cause the morphology change. Atomic force microscopy with the tip tethered with the polymer or parts of the polymer (PEG or PLA) determined the adhesion forces to individual faces of the single crystals. The adhesion forces were the strongest (264 nN) with the (001) surface, the weakest (~5 nN) with the (100) surface, and intermediate (170 nN) with the (010) surface.[27]

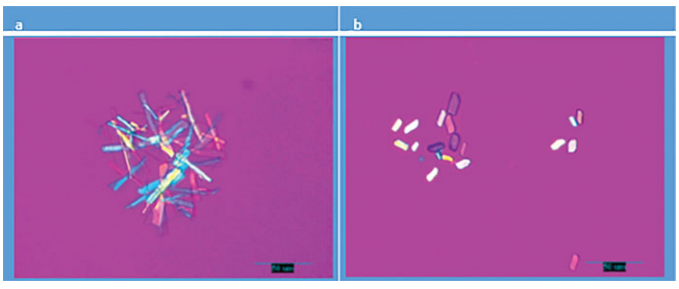

Figure 1. Tolazamide crystals obtained (a) in the absence of PEG-*b*-PLA and (b) in the presence of 50 μg/mL of PEG-*b*-PLA. Adapted from Kuldipkumar et al.[12] to with permission.

Our MD simulation was designed to investigate the interactions between TLZ crystals and PEG-*b*-PLA in water. Large crystal surfaces of (001), (010), and (100) were built, respectively, into a sizable water box. A representative PEG-*b*-PLA was constructed, first equilibrated with a 130-ns MS simulation in water and then added to the water box containing the crystals. The assembly was simulated for 50 ns to determine how the polymer molecule interacts with each crystal surface. The nature of the polymer interaction with TLZ molecules was quantitatively determined through hydrophobic, van der Waals (VDW), and electrostatic interaction energies. The results from the study strongly correlated with the reported experimental data, allowing an in-depth view of how the molecular interactions responsible for the crystallization inhibition take place at crystal–water interface. This correlation with experimental results established our MD simulation method, which will allow future applications of this method in studying other drug crystal–polymer interactions.

EXPERIMENTAL

Building the Crystals

The single crystal structure of TLZ (molecular structure in Fig. 2a) was taken from CABCUD01[28] in the Cambridge Structural Database (Cambridge, UK). The crystal system is triclinic with space group $P1$, $Z = 2$ and $a = 6.355$ Å, $b = 9.223$ Å, $c = 13.510$ Å, $\alpha = 101.104°$, $\beta = 92.80°$, and $\gamma = 85.72°$ (Fig. 2b). The molecules are dimerized by NH–O hydrogen bonds and dimers are packed together through VDW interactions only.[28] TLZ is poorly water soluble (intrinsic solubility of ~70 μg/mL), hydrophobic (Clog P of 2.69), and weakly acidic (pK_a of 5.9 assigned to the sulfonamide hydrogen).[12,29] Three virtual crystals were constructed from the unit cell using Mercury software (Mercury 2.3, CCDC 2001–2009) following our previous method[30] with some modifications. The (001) surface crystal was built by extending the unit cell at a, b, and c directions for 17, two, and eight times, producing the 17 × 12 × 2 crystal lattice. Similarly, the (010) and (100) surfaces were made at 17 × 2 × 8 and 2 × 12 × 8 unit cell repetitions (detailed in Table 1 and Fig. 3).

The crystals constructed above were prepared using Visual Molecular Dynamics Software (VMD, version 1.9, March 2011).[31] The topology and parameters of TLZ for the CHARMM27[32] force field were obtained from the Swiss

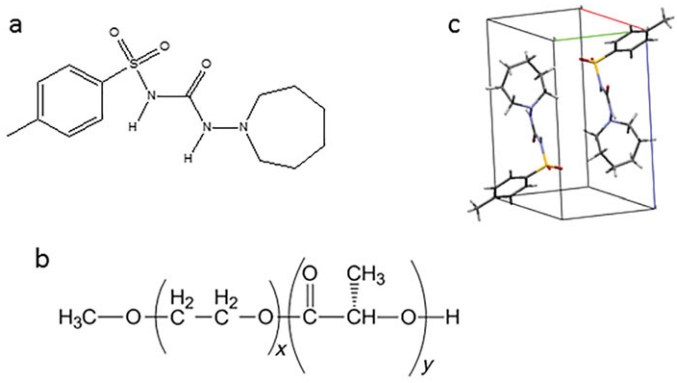

Figure 2. (a) Molecular structure of TLZ. (b) Unit cell of TLZ. (c) Molecular formula of PEG-*b*-PLA.