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Dissolution study of active pharmaceutical ingredients using molecular dynamics simulations with classical force fields

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ABSTRACT

The CHARMM, general Amber and OPLS force fields are evaluated for their suitability in simulating the molecular dynamics of the dissolution of the hydrophobic, small-molecule active pharmaceutical ingredients aspirin, ibuprofen, and paracetamol in aqueous media. The force fields are evaluated by comparison with quantum chemical simulations or experimental references on the basis of the following capabilities: accurately representing intra- and intermolecular interactions, appropriately reproducing crystal lattice parameters, adequately describing thermodynamic properties, and the qualitative description of the dissolution behavior. To make this approach easily accessible for evaluating the dissolution properties of novel drug candidates in the early stage of drug development, the force field parameter files are generated using online resources such as the SWISS PARAM servers, and the software packages ACPYPE and Maestro. All force fields are found to reproduce the intermolecular interactions with a reasonable degree of accuracy, with the general Amber and CHARMM force fields showing the best agreement with quantum mechanical calculations. A stable crystal bulk structure is obtained for all model substances, except for ibuprofen, where the reproductions of the lattice parameters and observed crystal stability are considerably poor for all force fields. The heat of solution used to evaluate the solid-to-solution phase transitions is found to be in qualitative agreement with the experimental data for all combinations tested, with the results being quantitatively optimum for the general Amber and CHARMM force fields. For aspirin and paracetamol, stable crystal–water interfaces were obtained. The (100), (110), (011) and (001) interfaces of aspirin or paracetamol and water were simulated for each force field for 30 ns. Although generally expected as a rare event, in some of the simulations, dissolution is observed at 310 K and ambient pressure conditions.

1. Introduction

The cost of developing a novel drug candidate is reported to be approximately US$ 800 million, increasing at an annual rate of 7.6% [1]. Computer simulations have largely changed the process of drug development in recent decades; thus, retarding the growth of pre-clinical costs [1]. Statistical methods, such as comparative molecular field analysis (CoMFA) [2,3], are commonly applied to discover active pharmaceutical ingredients (APIs). The docking of ligands [4] and target protein [5] has also been extensively investigated using molecular dynamics (MD) simulations. A current overview of molecular simulation techniques in the pharmaceutical sciences has recently been published [6]. Taft et al. [7] further highlight the close interaction between experimental and simulation techniques present in today's research. From a pharmacokinetics viewpoint, issues may arise when drugs are administered orally in a crystalline state [8]. While crystallization is a valuable step in production, it may lead to serious drawbacks in drug activity. Due to the high hydrophobicity of many APIs, pharmaceutical engineering aims at improving API dissolution behavior [9]. On the way to further understanding the mechanisms behind dissolution at the molecular scale, we evaluated the suitability of classical force fields for molecular dynamics simulations of small, hydrophobic API molecules.

In the last decade, model compounds, such as urea and glycine, have been studied extensively by computational methods. Piana and Gale [10] have published a molecular dynamics and kinetic Monte Carlo (kMC) simulation study on urea dissolution and growth. Studying the crystal growth of glycine from an aqueous solution, Banerjee and Briesen [11] monitored dissolution rather than growth under supersaturated conditions. Further force field development was proposed by Cheong and Boon [12]. Comparing different force fields and charges, they found the heat of solution to be an important criterion when modeling the glycine crystal

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growth. Li et al. [13] have studied the interaction of aspirin molecules in an aqueous solution at the crystal–liquid interface, using the lattice parameters to test the force field suitability. In this paper we evaluate the suitability of these parameters for the molecules aspirin, ibuprofen and paracetamol. To account for the increased flexibility on the interfaces, the rotation and the translation of molecules on the interface served as additional measures. Finally, 30 ns simulations for all molecules and all force fields for different interfaces are performed.

The difficulty in choosing a suitable force field mainly arises from the strict focus of most common force fields on particular properties. While accurate simulation of proteins in an aqueous solution is crucial for studies of topics such as ligand docking [14,15], mineral force fields may have a stronger focus on crystalline structure representation for single compounds, or even on polymorphic forms [16]. For dissolution, a force field is supposed to represent the crystal structure just as accurately as the interaction of solute and solvent molecules. The suitability of a force field, thus, not only depends on the molecule of interest but also on its specific environment within the simulation. Herein, since the diversity of the force fields available hinders the provision of a comprehensive review, this study focuses on force fields for which software packages and online resources are provided to facilitate the generation of force field parameter files for common simulation packages [17,18]. No experimental inputs other than the crystallographic structures were used in this study, which makes the technique easily accessible for novel drug candidates. Structural, thermodynamic and interface-specific parameters were evaluated to make a proper choice in force field selection.

While the API molecules studied in molecular dynamics simulations thus far mostly exhibit good solubility in water [10–12], this work focuses on small-molecule drugs with low aqueous solubilities for which poor dissolution kinetics might correspondingly be suspected. Specifically, aspirin, ibuprofen, and paracetamol are chosen as model substances as they all are experimentally well characterized. Their chemical and the corresponding experimental unit cell structures are shown in Fig. 1. They exhibit a considerable number of degrees of freedom and form single hydrogen bonds (paracetamol) or pairs of hydrogen bonds (aspirin and ibuprofen). Moreover, aspirin and ibuprofen form hydrogen bonds between two molecules, whereas a network of hydrogen bonds is formed within the paracetamol crystal structure. In contrast to aspirin, which exhibits a rather compact structure, ibuprofen has an elongated structure.

This study evaluates the force fields under consideration on the basis of their capabilities to reproduce the correct crystal lattice parameters, to describe the molecular interaction energies of configurations identified as typical in the crystalline structure (Section 3.1), and to reproduce the kinetics (Section 3.2) and thermodynamics (Section 3.3) on solvent–solute interfaces. Finally, the results of the 30 ns simulations are presented in Section 3.4.

2. Computational details

The unit cell representations of the model substances aspirin (form I) [19], ibuprofen (racemic, form I) [20], and paracetamol (form I) [21] were taken from the literature. The CHARMM force field parameters were generated using the SWISS PARAM server [18]. The ACEPYPE [17] software based on the ANTECHAMBER [22] software package was used to obtain the general Amber (GAFF) [23] force field parameters. The commercial program Maestro from the SCHRÖDINGER software package [24] was used to produce the OPLS-AA (OPLS) [25,26] force field files. The water models [27] used were TIP3P for CHARMM and GAFF, and TIP4P for OPLS simulations, as advised by the GROMACS software package, with which all MD simulations were performed [28].

Long-range electrostatics were calculated with the particle-mesh Ewald method [29]. Van der Waals interactions were truncated at distances of 1.2 nm (CHARMM), 0.9 nm (GAFF), or 1.4 nm (OPLS). For the neighbor-list and the real space cut-off distances values of 1.2 nm (CHARMM) or 0.9 nm (GAFF and OPLS) were used. These are the parameters used in the original parametrizations of the force fields and have shown good performance in the literature [30]. The timestep used in all simulations was 2 fs, with the bonds constrained using the LINCS algorithm [31]. A Nosé–Hoover thermostat [32,33] and a Parrinello–Rahman barostat [34] were used to sample the isothermal–isobaric ensemble at 310 K and 1 bar. During equilibration simulations, the Berendsen method [35] was applied to control the temperature and/or pressure.

Due to the lack of an algorithm for unit cell relaxation in the GROMACS package, the optimization of the bulk crystal structures and the corresponding lattice parameters was performed, starting from the experimental crystal structure, by slowly cooling the system from 100 to 0 K in a 50 ps simulation while applying a Berendsen barostat at zero pressure. In detail, the barostat was coupled to the lengths of the cell vectors as well as to the β-angle, whereas the remaining two angles were fixed to preserve the monoclinic crystal system. After the optimization of the cell vectors, all atomic positions were again relaxed using the conjugate gradient method with a maximum force threshold of 0.01 eV/Å. Apart from fixing the α- and β-angles during the MD simulations, no additional symmetry constraints were imposed on the structure for the optimization procedure. The starting

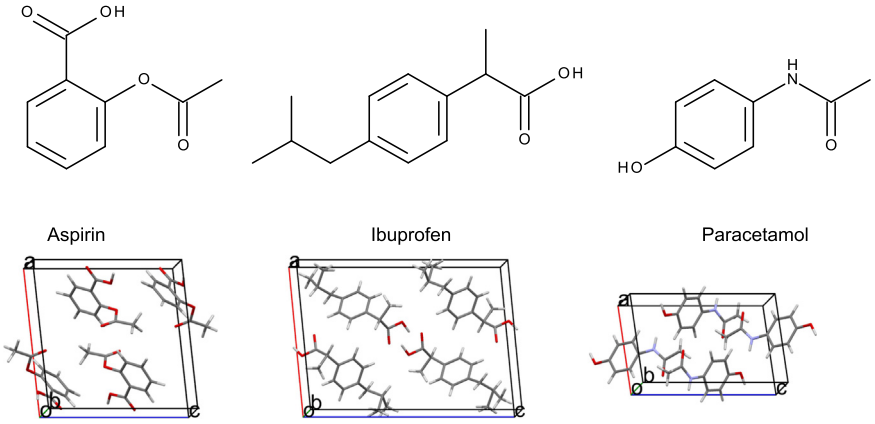

Fig. 1. Chemical and experimental unit cell structure of aspirin [19], ibuprofen [20] and paracetamol [21].