ABSTRACT

Parks, Conor D. Ph.D., Purdue University, May, 2017. A Molecular Dynamics Investigation of Solid-State Form Prediction, Selection, and Control. Towards Application to Crystallization. Major Professor: Doraiswami Ramkrishna

Polymorphism, the ability of a molecule to self-assemble into multiple solid-state forms, intimately determines the solid-state properties of a material. In the multi-trillion dollar pharmaceutical industry, where 90% of all products are sold in the solid-state, this has tremendous implications for key tablet properties such as shelf life, bioavailability, dissolution, nucleation, and growth rates. This myriad of performance variables frequently leads to competing design interests. This is exhibited by the frequently observed case of the most stable solid-state form displaying insufficient bioavailability *in vivo*, requiring the manufacturing of a more bioavailable, yet less stable, polymorphic form. Furthermore, it is well known that while a particular polymorph may be more thermodynamically stable, its rate of formation (kinetics) may be slower relative to its metastable counterpart. Consequently, a pharmaceutical crystallization process that has been designed to produce only the desired stable polymorph may result in different, or worse yet, undiscovered, polymorphic forms, due to unforeseen variations in the manufacturing process conditions. These examples illustrate the importance of understanding polymorph formation and control to allow for optimal polymorphic form selection and manufacturing.

Current methods of polymorphic form manufacturing and discovery, which include solution crystallization and solid-form screening, lack the appropriate level of atomic insight required to fully understand the crystallization process, require the use of costly API materials during screening, and never fully answer the question of whether all polymorphic forms have been discovered. As such, predictive simulation methodologies are desired to alleviate these issues. Although, molecular dynamics (MD), a simulation methodology which time integrates Newton’s equations of motion with fully atomistic detail, provides the necessary predictive capability, it has suffered from time scale

challenges associated with activated rate processes, such as nucleation, as well as the large system sizes (>100 K atoms) necessary to simulate solution crystallization, hence limiting its use for relevant API molecules. Prior to this thesis, only a handful of attempts to screen the crystallization of organic molecules have been performed.

This thesis addresses the aforementioned computational and methodology limitations of MD, and demonstrates that MD can serve as an *in silico* screening tool for the prediction, selection, and control of polymorphic forms through atomistic insights. Hence, this work represents an essential step towards fully atomistic, *in silico*, design of an industrial crystallization unit. Specifically, it is demonstrated that MD can predict polymorphic form crystallization from solution, nanocrystal dissolution kinetics and solubility increase, and finally the influence of an externally applied electric field (e-field) on crystallization dynamics, crystal morphology, and polymorphic form. To make these simulations computationally accessible for the first time, a newly developed massively parallel MD engine, specifically designed for Intel® Xeon Phi™ coprocessor hardware, is used as an investigative tool. This allows simulations with fully atomistic detail and femtosecond resolution to be performed, yielding insights into the diverse physical phenomena associated with polymorphism. It is demonstrated that polymorph specific nucleation kinetics and solubility calculations allow for the correct prediction of both glycine and paracetamol polymorphs at the nanoscale and bulk (micron) length scales, in aqueous solution, through the use of the seeded cluster simulation methodology. Furthermore, nanocrystal dissolution kinetics calculations are shown to predict the fastest dissolving polymorph of glycine, and hence allow for the selection of the polymorph with highest potential bioavailability *in vivo*. Finally, externally applied, static, e-fields are demonstrated to be a significant control variable over nanocrystal growth and dissolution dynamics, allowing for the manipulation of particle size distributions by varying the e-field intensity alone. The morphology of nanoparticles grown in the presence of the e-field vectors is shown to be needle like, with principal axis either perpendicular (paracetamol) or parallel (glycine) to the applied e-field vector. Most importantly, it is demonstrated that e-fields allow for the formation of never before seen paracetamol and glycine crystal structures that maximize the alignment of solid-state molecules with the

applied e-field vector. This enhanced scope for control of crystal structure with novel properties should serve the unparalleled quest for advanced materials in industries as diverse as alternative energy, pharmaceuticals, and defense.