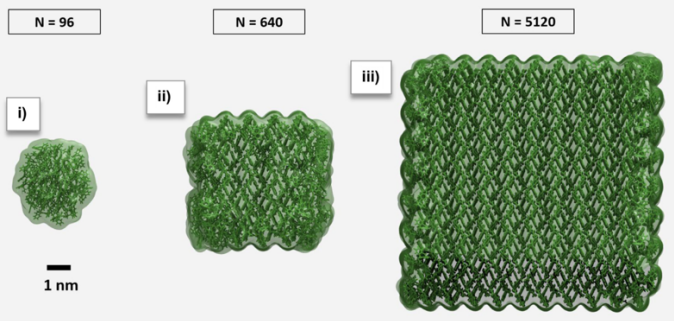
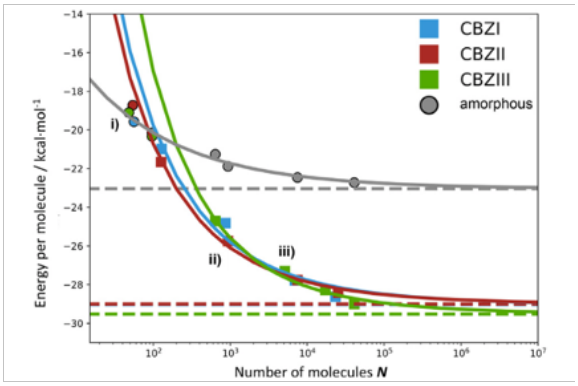
Molecular Modelling of Drug Formulation: From “tailor-made” Force Field to Stability Analysis of Carbamazepine Crystals

Moritz Macht

Friedrich-Alexander-University Erlangen-Nuernberg, Naegelsbachstr. 25, 91052 Erlangen, Germany

The polymorphism of drug crystals can be a challenging hurdle in drug formulation as in the case of Carbamazepine (CBZ) [1]. Decades of experimental studies were necessary to identify and rank the different polymorphs of CBZ, while also trying to enable a control on the formulation of CBZ. Meanwhile advancement in molecular simulation opens a window to techniques for prediction of polymorphs of newly developed drugs without the need of experimental data [2]. Therefore, molecular modelling provides exiting perspectives in the field of computer-aided drug formulation [3].





Starting with the generation of force field by minor tailor-made improvements to the widely established GAFF force field model, we outline a blueprint to adjust the general force field (FF) to a specialized use case. By analysis and optimization of single molecule interactions up to the bulk crystal systems, the intricacies of interactions in the model system and their respective interplay are elucidated.

With the help of molecular dynamics (MD) simulations, melting enthalpies are determined in comparison to experimental data. Despite inherent limitations of MD simulations in accuracy due to various factors, the gained insights of the MD simulations and the resulting elucidation of possible polymorphism control factors are presented.

In addition to the characterization of bulk systems, an outline of size dependent stability profiles is presented and shedding light onto the energy contributions of bulk, surface, and edge terms for the CBZ system with promoting different polymorphs under differing size confinements. Based on these findings a multi-step nucleation mechanism is proposed with varying aggregate behavior dependent on aggregate size [3,4].

[1] A. Grzesiak, M. Long, K. Kim, et al., *J. Pharm. Sci.*, **2003**, *92(11)*, 2260-2271.

[2] J. Anwar, D. Zahn, *Adv. Drug Deliv. Rev.*, **2017**, *117*, 47-70.

[3] A. Gadelmeier, M. Macht, D.Zahn, *J. Pharm. Sci.*, **2022**, *111(10)*, 2898-2906.

[4] D. Zahn, *ChemPhysChem*, **2015**, *16(10)*, 2069-2075.