Poster Presentation

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Interpreting Disordered PXRD Structures using Molecular Dynamics

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A central topic in the formulation of solid medicinal products is the identification of a suitable solid form of an active compound to obtain optimal physicochemical properties. To this end, disorder may be important for relevant crystal properties like stability. For example, disorder may account for more than 10% of the crystal volume. A rational approach to solid-form selection is typically based on structural information at atomic resolution. In practice, pharmaceutical compounds are not always well-behaved and especially in the study of polymorphs or compounds with flexible groups it can be challenging to obtain crystals suitable for single-crystal X-ray diffraction. Powder X-ray diffraction (PXRD) is a popular alternative, but it generally requires supplementary information like molecular connectivity in simple cases or computational models to solve larger structures. Computational modeling has come a long way and accurate and reliable structures of pharmaceutically relevant compounds can indeed be obtained using laboratory PXRD measurements and quantum-mechanical calculations [1]. The major limitation of quantum mechanical calculations, however, is that they do not consider time nor temperature but only static structures at zero temperature. Thus, these methods cannot model phenomena related to disorder. The molecular dynamics (MD) method can add temperature as well as time and spatial resolution to a model and has in recent years developed to be a scalable, reliable and increasingly available technique. As more and more groups from academia as well as industry employ MD in their work, the development will increase to gain momentum in the coming years. We use MD in a high-performance setting to study crystal properties that are relevant for pharmaceutical research. Using a combination of models from first principles and MD we are able to study highly disordered structures and polymorphs on the basis of PXRD data.

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