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Development of molecular dynamics models of complex crystallisation mechanisms of pharmaceuticals

Molecular modelling can give critical insight into the properties and behaviour of pharmaceutical crystals. Classical Molecular Dynamics enables modelling large systems accounting for solvent and thermodynamics effects. It also provides time resolved information otherwise inaccessible to stationary DFT calculations or Monte Carlo (simulations).

In the present work, we will discuss our development of molecular dynamics (MD) models for studying the interaction of excipients with crystalline nanoparticles of drug products. We will start by showing a test case of the nucleation of an active pharmaceutical ingredient (API), flufenamic acid (FFA), in ethanol. Through the CHARMM/CGenFF forcefield and GROMACS engine, we have been able to model the interactions between FFA and ethanol. A supersaturated ratio (1:12) and undersaturated ratio (1:36) of uniformly distributed FFA in ethanol, as well as a pre-built crystal of FFA in ethanol, also at the supersaturated ratio (1:12), were all modelled at room temperature and atmospheric pressure. Each of these systems were analysed for up to 1μs. By using MD, we can analyse how the change in ratio of FFA:Ethanol affects the for non-classical nucleation behaviour, as well as finding which state is best for mesoscale cluster formation; a crystal of FFA in ethanol that first dissolves and then reforms, or uniformly dispersed molecules of FFA in ethanol.

We have also used Classical MD to model the crystallisation of a different API, indomethacin using the LASP method (liquid-antisolvent precipitation). Experimentally there were challenges in obtaining the stable polymorphic form of the API. A seeding approach was experimentally successful in driving the solid-state transformation, which we then computationally redesigned. The two different excipient combinations that were successful in driving the solid-state form transformation also had to be modelled. Our aims were to model the impact and influence of the seeding approach on the system, as well as the difference between the two excipient combinations.

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