Real-time In-situ Synchrotron Study of Simvastatin Crystallization on Levitated Droplets

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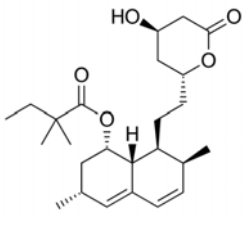
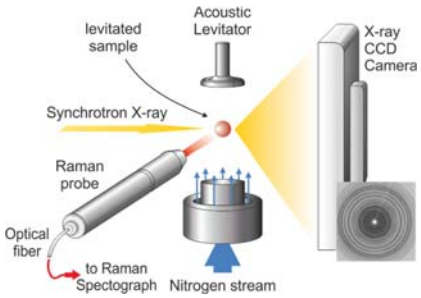
Simvastatin is one of the most widely used active pharmaceutical ingredients (API) for treatment of hyperlipidemias. The compound is known to exhibit polymorphism,[1,2] and also to exist in stable amorphous phases.[3,4] Controlling its crystallization from solution, therefore, becomes an important issue, to ensure the manufacture of an API with highly reproducible pharmaceutical properties (e.g. shelf-life, dissolution rate, bioavailability). There are, however, to the best of our knowledge, no systematic studies on how different solvents may change the pathway and outcome of simvastatin crystallization.

Here we describe a real-time and in-situ study of the crystallization of simvastatin at 297 K, in three solvents which differ in polarity and protic character: ethyl acetate, acetone, and ethanol. The studies were carried out by solvent evaporation, at the µSpot beamline (BESSY II, Berlin, Germany), using acoustically levitated solution droplets (contactless sample holder) in combination with simultaneous synchrotron X-ray diffraction, Raman spectroscopy, and imaging analysis. This multi-technique approach has proved to be a very powerful tool to follow the whole crystallization process in real-time and in-situ, and to identify intermediates preceding the final product.[5]

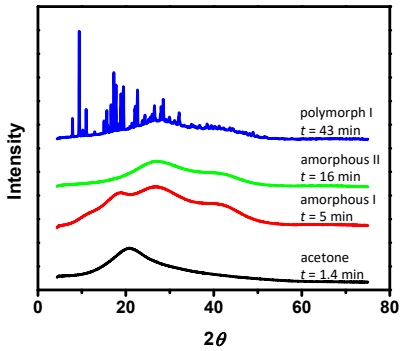
Significantly solvent dependent behaviour was observed: (*i*) in ethyl acetate, after solvent evaporation, a glassy material was formed, which crystallized on storage over a two-week period; (*ii*) in ethanol a gel was obtained; (*iii*) in acetone, a sequence of two different amorphous phases was found to precede the crystallization of polymorph I, which is the stable form of simvastatin at ambient temperature. The synchrotron studies were complemented by molecular dynamics simulations of the aggregation processes occurring in solution as solvent evaporates at constant temperature.



Simvastatin



Experimental set-up



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