Polymorphism in Simvastatin: Does it Affect Drug Performance?

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Studies of structure–energetics relationships in active pharmaceutical ingredients have received considerable attention due to its importance in the effective production and safe use of drugs. As most drugs are employed in solid formulations, attention must be paid to the characterization of the obtained crystalline structures (polymorphism), their stability domains, and the nature of the phase transitions between them. Even though the molecule is unaltered, different packing arrangements lead to different intermolecular interactions and, in turn, to variations in the physical and chemical properties of the solid (e.g. different colours, fusion temperatures or solubilities [1]). One emblematic example of the impact of polymorphism refers to the protease inhibitor drug Ritonavir, marketed for AIDS treatment. Two years after launch of the drug, the unexpected appearance and dominance of a new polymorph, which was considerably less soluble than the known form, forced the withdrawing of the product from the market, and threatened the supply of this lifesaving treatment, until a new formulation was obtained [2].

Simvastatin is one of the most widely used active pharmaceutical ingredients for the treatment of hyperlipidemias and is normally administered in a solid formulation. In this work, the crystal structures of the three known polymorphs were studied by single crystal X-ray diffraction, hot stage microscopy, and differential scanning calorimetry (Figure 1). Computational calculations (both by quantum chemistry and molecular dynamics simulations) were also performed to aid in the interpretation of the results. The transitions between the different forms were found to be fast and reversible, and thus different crystal structures are unlikely to be a problem for pharmaceutical formulations employing crystalline simvastatin.

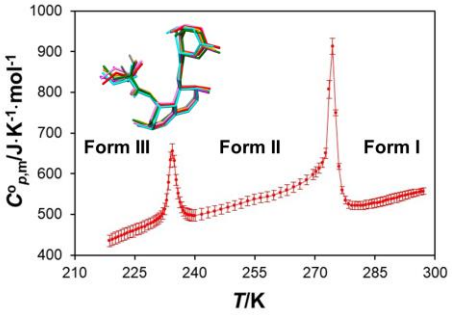

Figure 1. Heat capacities of solid simvastatin identifying the stability regions of each polymorph and overlay of the molecular conformation of simvastatin as a function of the temperature.

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