P1 Crystals, glasses, and gels: controlling solid state forms of simvastatin

Simões, Ricardo G.[A*]; Bernardes, Carlos E.S.[A]; Piedade, M. Fátima M.[B]; Diogo, Hermínio P.[B]; Minas da Piedade, Manuel E.[A]

A – Centro de Química Estrutural, Institute of Molecular Sciences, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade de Lisboa, Campo Grande, 1749-016 Lisboa, Portugal.
B – Centro de Química Estrutural, Institute of Molecular Sciences Instituto Superior Técnico, Universidade de Lisboa, Av. Rovisco Pais 1049 001 Lisboa, Portugal
*E-mail: rasimoes@fc.ul.pt

Simvastatin (**Figure 1**) is one of the most widely used active pharmaceutical ingredients (API) for the treatment of hyperlipidemias. The compound is employed as a solid in drug formulations. As such, particular attention must be given to the characterization of its different crystal forms (polymorphs), their stability domains, and the nature of the phase transitions that relate them. Modifications in crystal packing and crystallinity are commonly accompanied by significant changes in physical properties (e.g. variations in solubility), and may lead to serious problems in terms of reproducible preparation and safe use of a medicine. As a result, the characterization of structure−energetics relationships for solid APIs is of considerable importance in the pharmaceutical industry.
In this work simvastatin will be used as a model to illustrate how experimental (single crystal X-ray diffraction, hot stage microscopy, differential scanning calorimetry, and solubility measurements) and molecular dynamics results can be combined to guide the control of API production in specific solid state forms. Simvastatin has three known polymorphs. Form I is the thermodynamically stable one under ambient conditions and converts to the other two by fast solid−solid phase transitions (at 275.2 K for the form I → form II transition and 236.9 K for form II → form III). [1,2] Furthermore, long-lived amorphous phases of simvastatin have also been observed. [3]

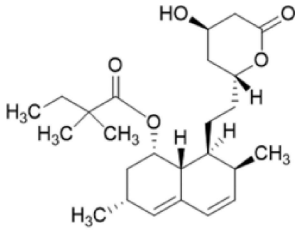

Figure 1. Molecular structure of simvastatin.

Acknowledgments: Centro de Química Estrutural is a Research Unit funded by Fundação para a Ciência e Tecnologia (FCT) through projects UIDB/00100/2020 and UIDP/00100/2020. Institute of Molecular Sciences is an Associate Laboratory funded by FCT through project LA/P/0056/2020. This work was also supported by the FCT project PTDC/QUI-OUT/28401/2017 (LISBOA-01-0145-FEDER-028401), and a postdoctoral grant awarded by FCT to R.G.S. (SFRH/BPD/118771/2016)..

References: [1] R.G. Simões, C.E.S. Bernardes, H.P. Diogo, F. Agapito, M.E. Minas da Piedade; *Mol. Pharmaceutics* **2013**, 10, 2713-2722. [2] R.G. Simões, C.E.S. Bernardes, A. Joseph, M.F.M. Piedade, W. Kraus, F. Emmerling, H.P. Diogo, M.E. Minas da Piedade *Mol. Pharmaceutics* **2018**, 15, 5349-5360. [3] T.G. Nunes, M.T. Viciosa, N.T. Correia, F. Danèle, R.G. Nunes, H.P. Diogo *Mol. Pharmaceutics* **2014**, 11, 727-737.