

## Solubility of Simvastatin in Acetone, Ethyl acetate, and Ethanol: An Experimental and MD Simulation Study

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### INTRODUCTION

The determination of the solubility of a compound in different solvents is, usually, an important step in the design of crystallization processes. When assisted by MD simulations, solubility determinations may also provide insights into how molecules assemble in solution to form crystals, a question whose elucidation remains a major chemical challenge.<sup>1</sup> The advantage of combining experimental and simulation results will be exemplified here using simvastatin (Fig. 1),<sup>2,3</sup> one of the most prescribed antihyperlipidemic drugs, as model system.

### DESCRIPTION OF THE WORK

The solubility of simvastatin in three solvents differing in polarity and protic character (acetone, ethyl acetate, and ethanol), was investigated through a combination of solubility vs temperature measurements, using UV-Vis spectroscopy and the solid residue method, and molecular dynamics (MD) simulations. X-ray powder diffraction (XRD) was also performed to analyse the solid phase in equilibrium with the solution.

### RESULTS AND DISCUSSION

The solubility order of acetone > ethyl acetate > ethanol, in the temperature range 283–308 K, was obtained. Although three polymorphs are known for simvastatin,<sup>3</sup> XRD analysis indicated that form I was always present in equilibrium with the solution throughout the experiments.

Higher solubility is generally assumed to be associated with low aggregation of solute molecules. In the case of simvastatin, however, MD simulations suggested that this is not necessarily true. Indeed, the results indicated that the observed solubility trend reflects a balance between the tendency for solute aggregation and the ability of the solvent to penetrate the aggregate structures, regardless of their size, and effectively establish solvent–solute interactions.

Finally, the obtained results contributed to resolve the very large discrepancies found between the previously reported solubilities of simvastatin in ethanol and ethyl acetate.<sup>4-6</sup>

### FIGURES AND TABLES

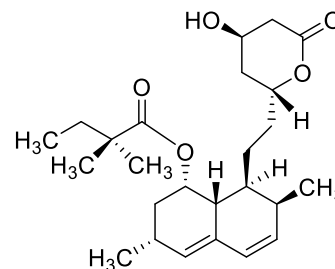


Fig. 1: Molecular structure of simvastatin.

**Acknowledgements:** This work was supported by the Fundação para a Ciência e a Tecnologia (FCT), Portugal (projects PTDC/QUI-OUT/28401/2017, LISBOA-01-0145-FEDER-028401, UIDB/00100/2020 and UIDP/00100/2020), and by the FCT-DAAD program for cooperation in science. A postdoctoral grant awarded by the FCT to R.G.S. (SFRH/BPD/118771/2016) is also gratefully acknowledged.

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