Title : **Tetramorphism of Fananserine : when a well defined strategy coupling state-of-the-art approaches in crystallography and thermodynamics also allows to elucidate complex polymorphism cases**

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Chemically pure organic molecular compounds can be found in two or more crystalline states. This corresponds to the phenomenon of polymorphism which is thus described as the ability of a molecule to crystallise in different structural arrangements. Given one temperature and one pressure, only one form is thermodynamically stable; however several forms are often isolated experimentally. Then, one of the main polymorphism-related problems is to establish a hierarchy of stability among these different crystalline phases.

Fananserine is a pharmaceutical compound for which four crystalline phases[1] ('to date') have been isolated over a period of six years. The forms (I, II, III and IV) were named according to their appearance order. It is a rare, if not original, example of tetramorphism, which is complete in structural and thermodynamical terms[2]. The structures of forms III and IV were solved from single crystal data, while those of forms I and II, available as microcrystalline powders, were solved from powder diffraction data collected with a conventional X-ray source using a simulated annealing technique (*PowderSolve*[3]) combined with a Rietveld refinement according to a procedure describe elsewhere[4,5]. The present study describes the different steps in the construction of the phase diagram (p-T) of this tetramorphism (20 *a priori* possible triple points). The construction method[6], which incorporates these crystallographic results combined with calorimetric data, is based on fundamental rules of thermodynamics : the Ostwald criterion of the lowest vapour pressure, the first law, the Clapeyron equation and the rule of the alternating stability (or metastability) of the two-phase equilibria forming a triple point. As only the fusion of each form was observed, the path used to construct the p-T diagram consisted first in determining the slopes of the solid-liquid melting curves, then in defining their intersections (triple points S_i-S_j-*l*) from which the linear equations for S_i-S_j curves were calculated. The temperatures of these equilibria, extrapolated at pressure 'zero', were assigned to triple points S_i-S_j-*v* (i and j define two among phases I, II, III and IV). From these in-depth study, it follows that phases II, III and IV have their own stability domain, whereas phase I is an intrinsically metastable phase for which a monotropic behaviour is inferred regardless of the phase region (stable or metastable) into which it is passing. The stability domains of phases II and III are limited in pressure by that of phase IV, which is the stable form at room temperature. This study shows how thermodynamics can be used to construct p-T diagrams for cases as complicated as this tetramorphism,[7] and how the stability ranking of polymorphs according to temperature and pressure can be inferred even if transitions are not experimentally observed.

These results also illustrate the synergy effect of combined analytical, physical and theoretical methods in the selection of potential candidates for the elaboration of a drug during the pharmaceutical development.

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