

**THE ELUCIDATION OF THE TETRAMORPHISM OF FANANSERINE
WITH X-RAY POWDER DIFFRACTION:
FROM PHASE CHARACTERIZATION TO PHASE DIAGRAM**

J. Giovannini^{1,2*}, M.-A. Perrin², D. Louër¹, S. Toscani³, R. Céolin³, F. Leveiller^{2*}

¹Institute of Chemistry of Rennes, LCSIM-CNRS, University of Rennes, France

²Aventis Pharma, Laboratoire de Physique Appliquée, Vitry-sur-Seine, France

³Laboratoire de Chimie Physique, University of Paris V, France

*present address: AstraZeneca R&D, Preformulation and Biopharmaceutics, Lund, Sweden

During the development of a drug compound, X-Ray Powder Diffraction (XRPD) is used from early stages, e.g. to estimate the batch crystallinity during the selection process, until in-depth structural and physical characterizations. The complexity of the investigation is increased when various modifications of the material appear and when single crystals of suitable quality are not available. Therefore, powder pattern indexing is often the cornerstone of the strategy to elucidate complex cases of polymorphism. Crystal symmetry and unit-cell parameters are obtained, from which a phase is identified, and, if further structural information is needed, indexing is the preliminary requirement to determine the atomic positions from powder diffraction data. Moreover, the objective being the knowledge of the most thermodynamically stable phase in ambient conditions, XRPD can play another major role in the elaboration of the phase diagram : volume changes can be evaluated from precise anisotropic thermal expansion XRPD studies and, then, can be combined with calorimetric data to determine the stability domain (according to Gibbs) for each identified phase through fundamental thermodynamics rules.

The role of XRPD to elucidate the polymorphism is illustrated here with fananserine, $C_{23}H_{24}N_3O_2SF$, a drug with a potential antipsychotic activity. In the solid state, this drug substance presents a complex case of tetramorphism, for which the four crystalline forms have been isolated over a period of six years. The crystal structures of forms III ($P2_1/n$) and IV ($P2_1$) were solved from single-crystal diffraction data, whereas those of forms I ($P-1$) and II ($P2_1$), which are available as powders only, were solved from XRPD data collected with a conventional X-ray source, using a simulated annealing approach combined with Rietveld refinements. The stability domain of each phase was subsequently determined in the pressure-temperature phase diagram. For the calculations, the Clapeyron equation was applied with calorimetric data and volume changes measured from XRPD.