X-ray Diffraction, Computational Chemistry, and NMR: A Multi-disciplinary Approach to Understanding the Pharmaceutical Solid-state

F. G. Vogt
Chemical Development, GlaxoSmithKline plc. King of Prussia, PA 19406, USA

A combined approach to solving solid-state structural problems for pharmaceutical systems is presented, using spectroscopic, diffractometric, and computational methods to understand and predict behaviour in the solid state. In the studies discussed here, multinuclear solid-state NMR (SSNMR) is used to gain information on local molecular structure, and is interpreted in conjunction with single-crystal x-ray diffraction data. Two types of computational approach are also employed: molecular mechanics methods (including molecular dynamics and Monte Carlo approaches) and density functional theory (DFT). The computational methods are used to understand solid-state dynamics and inclusion phenomena, calculate NMR chemical shielding tensors, assist in powder structure solution of crystal structures, and predict other useful properties. Studies of phase transitions and water dynamics in channel hydrate systems such as sodium N-(3-(aminosulfonyl)-4-chloro-2-hydroxyphenyl)-N'-(2,3-dichlorophenyl) urea hydrate are discussed in detail, including the use of isotope exchange from the vapor phase and subsequent SSNMR studies of deuterium, oxygen-17, and other nuclei [1]. SSNMR is also employed to probe hydrogen bonding environments and molecular conformation through 1D and 2D SSNMR analyses of the proton, carbon-13 and nitrogen-15 nuclei. The combined use of x-ray powder structure solution methods, DFT, and solid-state NMR is illustrated on a dimorphic pharmaceutical molecule, {4-(4-chloro-3-fluorophenyl)-2-[4-(methyloxy)phenyl]-1,3-thiazol-5-yl} acetic acid, which exhibits a room-temperature enantiotropic thermodynamic transition temperature. Other examples of channel hydrates as well as cocrystal systems are also briefly discussed. The ultimate goal of this work is to improve the structural understanding of complex pharmaceutical solid-state phenomena to ensure process control and product performance.

[1] F. G. Vogt, J. Brum, L. M. Katrincic, A. Flach, J. M. Socha, R. M. Goodman, and R. C. Haltiwanger, Cryst. Growth & Design, 6, 2333-2354 (2006).