Identification, Crystal Structure Solution and Refinement of Stable and Metastable Pharmaceutical Compounds by Powder Diffraction

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X-ray powder diffraction has developed over the past several years into a powerful technique for the elucidation of crystal structures[1]. Moderately complex structures can be solved from laboratory X-ray powder diffraction patterns; the most successful techniques involve the use of global optimisation methods such as simulated annealing where the degree of complexity is determined by the internal molecular flexibility and the number of independent molecules in the crystal structure[2-8]. Key to this success has been the active use of molecular topology which reduces the structure solution problem to one of determining the external rotational and translational degrees of freedom and the internal torsion angles. Typically the number of parameters that must be determined range from six (for a rigid body) to a current upper limit of around thirty to forty parameters for conformationally flexible molecules or multiple molecules in the asymmetric unit. State-of-the-art analysis can successfully solve structures that represent some of the currently most challenging pharmaceutical compounds.

A distinct but related challenge for powder diffraction is the determination of drug structures during synthesis with a view to determining metastable intermediates and transition pathways. This talk will outline recent work using high-throughput X-ray powder diffraction to determine the hydration and dehydration of familiar pharmaceutical compounds and establish a comprehensive structural description of the transformation processes involved.

There are several hundred organic structures in the crystallographic literature and the concern now is not their determination but the accuracy of the crystal structure itself. Powder data contain, in general, far fewer well-determined Bragg intensities that a single crystal experiment. The determination of thirty to forty parameters is not a major issue for most powder diffraction patterns. However, the accurate, independent determination of 150 accurate coordinates in a fifty atom structure is a very different issue. Indeed, there are few laboratory-based powder diffraction patterns that will yield this much information with high accuracy and even the majority of synchrotron experiments will struggle with more than 100 parameters. Most accurate crystal structures from powder diffraction data will therefore involve the judicious use of, inter alia, bond-length, bond-angle and planarity constraints. This, in turn, raises the question of whether powder diffraction data will be able to yield unexpected surprises in organic crystal structures. Fortunately, there is a solution to this issue. High quality diffraction patterns can be collected on high intensity, medium resolution neutron powder diffractometers such as GEM at ISIS in a matter of hours on fully protonated molecular materials. This not only yields accurate hydrogen positions but, in conjunction with high resolution X-ray diffraction data, can provide a full, accurate description of the crystal structure. This talk will focus on the range of organic materials that may be solved from powder diffraction data, the information content of a powder diffraction pattern in the context of the refinement of organic crystal structures, the necessity of reasonable constraints, the use of robust statistics and the combined use of X-ray and neutron powder diffraction data for accurate crystal structure analysis.

References

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