

## POWDER DIFFRACTION AND CRYSTAL STRUCTURE PREDICTION: A TWO-WAY RELATIONSHIP

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For the many pharmaceutical materials that are administered in crystalline form, crystal structure determines properties such as solubility, bioavailability and consequently their therapeutic index. Powder diffraction provides us with a tool by which a crystalline form can be both identified or monitored through fingerprinting, or in favourable cases, can be fully characterized through structure solution and refinement. In cases where structure characterization from powder data is not ideal where data quality is poor and indexing or structure solution approaches fail, it can be the combination of crystal structure prediction and powder diffraction that leads to successful structure rationalisation.

However, the combination of theoretical prediction and experimental powder methods is a “two-way relationship”. In our work, we have utilised the complementary nature of the two approaches to generate information that may not be available from the use of one technique alone, both by matching experimental to calculated powder data to aid the rationalisation of crystal structures generated in a prediction, or by using the predicted structure as a starting point for Rietveld refinement both in terms of lattice parameters and crystal structure<sup>1</sup>.

Among the many reasons for prediction of the crystal structure of a molecule prior to its synthesis, the prediction of possible polymorphs ranks among the most important, especially to the pharmaceutical industry. Often numerous structures are predicted within a narrow energy range, making absolute characterization of the crystal structure both difficult and sometimes impossible<sup>2</sup>. Identification of the experimental form among a large number of theoretical structures is normally done by visual comparison of the experimental powder data with that simulated from the predicted structures. This is a time consuming and often tedious process, making the development of a robust and reliable automated evaluation process vital as this combined theoretical/experimental approach becomes more established.

We will present our work towards the development of a reliable automated evaluation of predicted and experimental structures using a number of quantitative guides<sup>3</sup> (illustrated by examples including imidazole, chlorothalonil and 5-azauracil), and demonstrate the use of structure prediction in the crystal structure determination of anhydrous adenine. The effect of temperature differences between predicted and experimental structures and the resulting variation in lattice parameters on this automated process will also be discussed.

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