

STRUCTURES AND TRANSFORMATIONS IN PHARMACEUTICALS

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The physical characterisation of a pharmaceutical compound is an important step in the development cycle of a dosage form. A full range of analytical techniques is brought to bear on the problem, with the stability of the dosage form being of particular interest. In this regard, crystal form plays a key role that is usually investigated by thermal methods including DSC and TGA. Until recently, the use of XRPD in this area was largely confined to 'fingerprint' identification of material produced from crystallisation experiments. However, with the increasing use of variable temperature and variable-humidity sample environment attachments, XRPD is now gaining in prominence as a solid-state characterisation tool in pharmaceutical industry.

Nevertheless, in order to *fully* characterise and understand a compound's physical behaviour, determination of its crystal structure(s) remains an important goal. From a XRPD point of view, this is still a considerable challenge, even given recent developments in structure determination methodology. High-quality XRPD data, excellent sample environment control and a full complement of other physical characterisation data remain pre-requisites before a complete structural characterisation of a phase transformation can be attempted.

We have characterised the phase transformations of the hypnotic agent zopiclone using synchrotron XRPD data [1]. The monoclinic centrosymmetric form of zopiclone dihydrate undergoes a sequential, two-step transformation in the solid state upon heating, which results in the separation of enantiomers into a racemic conglomerate or racemic twins. Key to understanding the transformations at the molecular level was the need to produce a sharply diffracting sample of monoclinic anhydrous zopiclone and solve its crystal structure. The combination of high instrumental resolution, optimal data collection strategy and global optimisation structure determination maximised the chances of obtaining the required information.

Three recent methodological developments in the global optimisation approach to XRPD structure determination will also be discussed and illustrated with examples of pharmaceutical relevance.

[1] N. Shankland *et al.*, *Chem. Commun.*, 2001, 2204-2205.