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Pushing the limits of molecular crystal structure determination from powder diffraction data in high-throughput chemical environments

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Abstract Crystal structure determination from powder diffraction data (SDPD) using the DASH software package is evaluated for data recorded using transmission capillary, transmission flat plate and reflection flat plate geometries on a selection of pharmaceutical compounds. We show that transmission capillary geometry remains the best option when crystal structure determination is the primary consideration and, as expected, reflection flat plate geometry is not recommended for SDPD due to preferred orientation effects. However, the quality of crystal structures obtained from transmission plate instruments can be excellent and the convenience factor for sample preparation, throughput and retrieval is higher than that of transmission capillary instruments. Indeed, it is possible to solve crystal structures within an hour of a polycrystalline sample arriving in the laboratory, which has clear implications for making small molecule crystal structures more routinely available to the practising laboratory medicinal chemist. With appropriate modifications to crystal structure determination software, it can be imagined that SDPD could become a rapid turn-around walk-up analytical service in high-throughput chemical environments.

Keywords crystallography; crystal structure; X-ray powder diffractometry;

Introduction Small-molecule crystal structures are known to contribute enormously to drug development for both physicochemical and intellectual property reasons. Despite this, they may not be being used as much as they should be by the practicing medicinal chemist in the early stages of drug discovery (Groom & Cole, 2017). For example, ligand molecule conformations from small-molecule crystal structures provide very useful comparators with target-bound conformations, which can be used to optimise binding affinity. Additionally, understanding of intermolecular interactions in the crystal lattice can be used to suggest ways to break those interactions and improve the solubility of hits and leads. For at least these reasons, routine access to small-molecule crystal structures is therefore highly desirable. Currently, single-crystal X-ray diffraction remains the gold standard technique for crystal structure determination, but finding suitable conditions to grow a large enough crystal can prove too time-consuming and, all too often, only microcrystals can be grown. In this context, powder X-ray diffraction (PXRD) provides a valuable alternative for determining crystal structures.