Investigation of an X-ray Diffraction–Based Approach for Evaluating Crystal Habit

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Crystal habit (external morphology) of an active pharmaceutical ingredient (API) can significantly influence physical properties such as dissolution rate, filtration and drying behavior, powder flowability, and tabletability, even when the polymorphic form remains unchanged. Consequently, variations in crystal habit may contribute to batch-to-batch variability in manufacturability and product quality. Therefore, continuous monitoring and, where necessary, control of crystal habit from development through manufacturing are important.

Conventionally, crystal habit has been evaluated primarily by optical microscopy, which allows direct visualization of crystal morphology. However, microscopic observation is inherently limited to a small portion of the sample, making it difficult to assess whether the observed crystals are representative of the entire batch. In addition, ensuring reproducibility and quantitative comparison can be challenging, which may limit its suitability for routine monitoring.

In this study, we investigate powder X-ray diffraction (PXRD) and single-crystal X-ray diffraction (SCXRD) as complementary approaches for evaluating crystal habit. PXRD is widely employed for solid-state characterization and enables rapid, non-destructive acquisition of diffraction data representing a large population of crystallites. When measurement conditions are carefully controlled, PXRD also facilitates reliable batch-to-batch comparison. Because diffraction intensities can be affected by preferred orientation arising from crystal morphology and sample packing in the holder, changes in peak intensity ratios in PXRD patterns may serve as practical indicators of differences in crystal habit. In this work, we describe an approach for evaluating crystal habit using PXRD, supported by structural insights obtained from SCXRD.