ADVANCES IN QUANTITATIVE PXRD: IMPROVING RESOLUTION FOR MULTI-COMPONENT SYSTEMS USING CONTEMPORARY CHEMOMETRIC METHODS

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Powder X-ray diffraction (PXRD) is a key analytical tool used for solid state haracterization of small molecule organic materials, having widespread use in the analysis of pharmaceutically relevant systems. Quantitative applications of PXRD also provide the advantage of non-destructive use with numerous sample configurations, allowing detections of subtle changes in materials as they respond to the physical manipulations required by pharmaceutical dosage form manufacturing. Historically, quantitative PXRD has been done using univariate methods whose sensitivity can be affected by low signal-to-noise ratios and low peak resolution. These problems are exacerbated to varying degrees depending on the configuration of the sample, but can be particularly pronounced for *in situ* evaluations of intact compacts or tablets.

Quantitative chemometrics, which uses multivariate linear regression and function estimation to relate analytical data to the properties of a system, has, over the last 20 years, become a mainstay for many types of quantitative spectroscopic data analysis. Through weighted combinations of signals from multiple channels, measurement noise and confounding factors having structured error covariance can be suppressed, allowing more subtle features of the data to be evaluated. Despite the fact that chemometric data analysis techniques have been applied to enhance analysis from numerous spectroscopic methods, their use in quantitative PXRD analysis has been comparatively limited.

Here we utilize multiple characterization techniques to investigate the applicability of multivariate processing for both diffraction and spectral data using contemporary chemometric methods. In particular, we specifically examine the quantitative power of various algorithms to characterize factors in the signals that can separate variance attributable to the physics of compact preparation from that due to alterations in phase composition in complex systems. A combination of PXRD, NIR spectroscopy, Raman spectroscopy, and terahertz pulsed imaging (TPI) were used to model quantitative compositional variations, as well as physical variations of a model four-component system consisting of two crystalline and two amorphous materials. Quantitative models for composition were generated using each of the characterization methods. Each technique was suitable for quantitative measurements, although each had its own limitations where method sensitivity was concerned. Models generated from variations in spectroscopic signal attributable to NIR spectroscopy and TPI were also successfully used to probe variations in compact density (as a function of compaction pressure), where similar correlations are being sought with respect to similar physical features in PXRD data.