QUANTITATIVE MULTIVARIATE APPLICATIONS IN PXRD OF INTACT MULTI-COMPONENT CONSOLIDATED PHARMACEUTICAL SYSTEMS

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Purpose. To demonstrate the suitability of multivariate calibrations in quantification of multi-constituent pharmaceutical dosage forms analyzed intact via powder X-ray diffraction (PXRD) using both reflectance and transmission geometries.

Methods. A model four-component system was developed consisting of two crystalline materials (anhydrous theophylline and lactose monohydrate), and two disordered materials (microcrystalline cellulose and starch). Powder mixtures of varying composition were compressed into 13 mm cylindrical compacts varying in the 67.0 – 268.1 MPa compression range. The compacts were analyzed by powder X-Ray diffraction in both reflectance and transmission geometries, using a PANalytical X'Pert Pro MPD with Cu K_α radiation (λ = 1.5406 Å). Quantitative models of composition were estimated using traditional univariate calibrations and compared with multivariate methods including principle components regression (PCR), classical least squares regression (CLS), and partial least squares regression (PLS) over entire diffraction patterns (corrected for axis shift).

Results. The lack of distinct Bragg diffraction peaks in the powder patterns inhibited the univariate estimation of the disordered components' concentration. Therefore, quantitative univariate models were generated for the two crystalline components. The average R^2 values for the crystalline components were 0.895 and 0.935 for reflectance and transmission geometries, respectively. Quantitative multivariate models were generated using CLS, PCR, and PLS. In the case of the crystalline components, transmission geometry showed superiority in accuracy with R^2 values of 0.959, 0.958, and 0.966 obtained from models calculated using CLS, PCR, and PLS, respectively. For the disordered components, a slight advantage in accuracy was observed using reflectance geometry with R^2 values of 0.959, 0.967, and 0.980 obtained from models calculated using CLS, PCR, and PLS, respectively.

Conclusions. The use of PXRD in the analysis of intact compacts comprised of multiple constituents remains an important mainstay in the pharmaceutical industry. The traditional univariate calibration methods for phase/constituent concentration determination do not possess the ability to quantify disordered components due to the lack of distinct Bragg diffraction peaks. Multivariate modeling improves parameters such as signal-to-noise, sensitivity, and selectivity lending to a greater advantage in quantification of low-diffracting disordered constituents. The increased accuracy of transmission geometry in quantification of crystalline components can be explained by the increased diffraction intensity attributed to a larger irradiated sample volume. The increased accuracy of the reflectance geometry in quantification of disordered components may be due to the increased angular resolution associated with this geometry.