CHEMOMETRIC APPLICATIONS IN QUANTITATIVE X-RAY POWDER DIFFRACTION OF INTACT CONSOLIDATED SAMPLES

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Purpose. Demonstrate the suitability of reflectance and transmission geometry multivariate calibrations in quantitative X-ray powder diffraction (XRPD) of intact quaternary pharmaceutical compacts.

Methods. Quaternary compacts consisting of two crystalline materials (anhydrous theophylline and lactose monohydrate), and two disordered materials (microcrystalline cellulose and starch) were prepared. Mixtures of varied composition were compressed into 13 mm cylindrical compacts at pressures ranging from 67.0 – 268.1 MPa. Compacts were analyzed by XRPD in reflectance and transmission geometries, using Cu K_α radiation (λ = 1.5406 Å, 2-60º 2θ, 0.02º step, 45.0 kV, 40.0 mA). Quantitative models of composition were estimated using univariate calibrations, which were 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 nonlinear axis shift).

Results. Quantitative univariate models for the two crystalline components resulted in R^2 = 0.895 and 0.935 respectively for reflectance and transmission geometries. Quantitative multivariate models, were generated using CLS, PCR, and PLS. Superior linearity in transmission geometry was observed for crystalline components (R^2 = 0.967, 0.969, and 0.973 respectively from CLS, PCR, and PLS models). Linearity was slightly improved for disordered components using reflectance geometry (R^2 = 0.928, 0.927, and 0.951 respectively from CLS, PCR, and PLS models). All multivariate models, which demonstrated significantly improved signal-to-noise, sensitivity, and selectivity relative to univariate models, were able to predict compositions of both disordered and crystalline phases; CLS was the most successful owing to its ability to generate regression vectors highly correlated to the pure component diffraction patterns.

Conclusions. Traditional univariate XRPD calibrations for quantitative phase determination cannot discriminate between different disordered components. Multivariate modeling improves signal-to-noise, sensitivity, and selectivity, improving the quantitative power of low-diffracting disordered constituents. The increased accuracy of transmission measurements for crystalline components is afforded by a larger irradiated sample volume, while increased accuracy of the reflectance measurements for disordered components is likely due to increased angular resolution.