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By

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New Methods for Extracting Information From Continuous Manufacturing Processes Through Real Time Spectroscopic Analysis

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New Near Infrared Spectroscopy (NIRS) spectroscopic methods were developed for real time determination of powder density and to estimate the total sampling error (TSE) in continuous blending processes. Powder density is a critical property in the manufacturing of solid oral dosages that affects tablet mass, hardness and dissolution. The establishment of calibration techniques for powder density resulted in the new strategies to control the amount of active pharmaceutical ingredient delivered to patients. In a second series of studies, variographic analysis was developed for determining the sampling error for pharmaceutical blends. The error of each analytical method is reported routinely in the pharmaceutical industry but the sampling error is not determined. Variographic analysis proposed in this work allows the implementation of correct sampling methodologies and the estimation of TSE.

Three different techniques were evaluated to obtain the required variation in powder density for calibration sets: 1) different tap density levels (for a single component), 2) generating different strain levels in powders blends (and as consequence powder density), through a modified shear Couette Cell, and 3) applying normal forces during a compressibility test with a powder rheometer to a pharmaceutical blend. For each variation in powder density, near infrared spectra were acquired to develop partial least squares (PLS) calibration models. Calibration models from the three approaches were tested by replicate experiments and by using a pilot plant with the NIR attached to an interface right after the continuous mixer exit. Calibration models were also developed to determine the Active Pharmaceutical Ingredient concentration for continuous

blending. With real time predicted values of concentration, variographic analysis was implemented and parameters, nugget effect, sill and range were identified.

All test samples from replicate experiment were projected inside PLS calibration set with relative standard error of prediction of 0.38%, 7.65% and 0.93% for tap density (single component), shear and rheometer respectively. Continuous blending experiments were successfully projected inside the tap and shear calibration models for powder density. First derivative was the data pretreatment with the lowest error of prediction, indicating the strong relationship with the spectral slope.
Powder rheometer did not reproduced the powder density variation at the continuous mixer exit, with possible applications in unit operations where powders receives normal forces such as feeders, and die filling in tablet press.

The variographic analysis indicated the presence of sill higher than the nugget effect. With this information of MPE, suggestion of blending improvements can be addressed for many others pharmaceuticals formulations.