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RESEARCH ARTICLE

Online Monitoring of Pharmaceutical Materials Using Multiple NIR Sensors—Part I: Blend Homogeneity

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Abstract

Introduction The present article discusses the implementation of a semi-automated blend homogeneity control system by two near-infrared spectrometers.

Methods A statistic was introduced to combine blend trends output by individual instruments based on the root mean squared error from the nominal value calculation. The necessity to monitor homogeneity at more than one location of a V-blender is highlighted and the impact of sensor and model differences on blend trends was evaluated. Using two different formulations, classical least-squares based models were developed to monitor blending. Calibration transfer between the two sensors was demonstrated as a useful approach when more than one sensor is used. Several classical transfer methods were implemented (optical, post-regression correction, and orthogonalization based) to balance the two sensors.

Results and Conclusion Results showed that the use of only one calibration model, transferred to all units monitoring the process was highly beneficial to achieving consistent results. Specifically, standardization methods targeting instrument differences were demonstrated to be the most successful. However, results showed that the optimization of a given transfer method was formulation-dependent.

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Introduction

The control of blend homogeneity has been improved in recent years with the development of process analytical technologies [1, 2]. Thief sampling followed by quantitative assay [3] has progressively been replaced by online blend monitoring methods. Near-infrared spectroscopy (NIRS) has become the method of choice for determining blend end-points and controlling mixing profiles for many drug products systems [4]. Additionally, formulation scientists use NIRS to understand mixing properties of the powders and manufacturing engineers rely on prediction trends of active pharmaceutical ingredient(s) (API) and excipients to stop the blending process in a timely and reliable manner.

The determination of the blend end-point is critical and many qualitative and quantitative approaches are available in the literature. Qualitative methods are based on the evolution, or rather the lack of evolution, of the spectral shapes over time. The first qualitative online blend monitoring was based on the calculation of a moving window standard deviation at each wavelength of three subsequent spectra, followed by the determination of an overall standard deviation plotted against time [5]. Later publications used dissimilarity index, principal component analysis, and soft independent modeling of class analogies [6], Hotelling's T^2 statistic [7], and principal component modified bootstrap error-adjusted single-sample technique [8]. In contrast, quantitative approaches rely on developing a regression model to measure the levels of the element(s)