Assessment of Lean Chemometric Techniques for Tracking Pharmaceutical Blend Uniformity

A. J. Rish[1], O. Rehrauer[1], S.V. Hammond[2], P. Doherty[3]

[1]Sentronic US Corp, [2]Steve Hammond Consulting, [3]Acuitis Process Analytical Technology Ltd

INTRODUCTION

Blend uniformity (BU) of pharmaceutical powder mixtures is a common critical quality attribute in oral solid dose (OSD) pharmaceutical manufacturing. Conventionally, thief sampling of material and subsequent off-line analysis by chromatography is used to assess BU of bin-blended OSD formulations, but has notable downsides: disturbing the powder bed can produce segregation, proneness to sampling errors, and requirement of waiting on laboratory results to confirm BU. Spectroscopic near-infrared (NIR) process analytical technology (PAT) has arisen as an alternative strategy for on-line monitoring of the bin blending process to generate process insights, enabling non-destructive and rapid verification of BU.

However, some conventional chemometric techniques that convert PAT data into BU information require a lengthy time investment and high costs to calibrate. The challenge of calibration burden in NIR PAT-based BU assessment has prompted the use of *lean chemometrics*: fit-for-purpose techniques that minimize the burden of calibration. Rate-of-change measurements, such as the moving block (MB) F-test, are a common choice of lean chemometric technique for BU monitoring. Pure component methods are calibration-free techniques that can provide qualitative and quantitative BU information from the spectra but have not been widely assessed for these applications. An emerging pure component method, the iterative optimization technology (IOT) algorithm, was compared with MB F-test and principal component analysis (PCA) for qualitative monitoring of the blending dynamics for a pharmaceutical drug formulation using a SentroPAT BU II NIR spectrometer to determine the suitability of pure component methods as lean chemometric techniques for BU monitoring.

METHODS

Pre-Blend → Main Blend → Lubrication

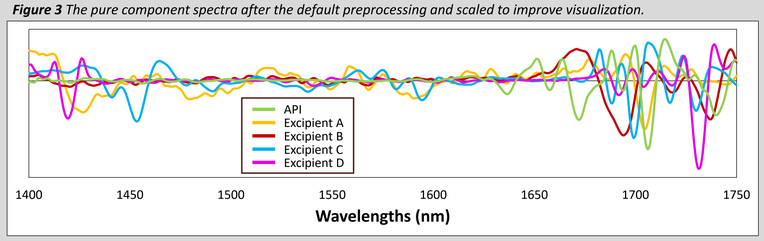
Figure 1 *Stages of the bin blending process under investigation by NIR spectroscopy*

The blending dynamics of a pharmaceutical powder mixture during a three-stage bin blending process (**Figure 1**) was analyzed using NIR spectroscopy. Between the pre-blending and main blending stages, a screening step for the pharmaceutical powder mixture was implemented. The pharmaceutical powder under analysis consisted of an active pharmaceutical ingredient (API) at a target concentration of 10 %w.w and five excipients (A – E).

The NIR spectra of the chemical constituents and the bin blending process were collected using a SentroPAT BU II (**Figure 2**) from 1350 nm to 1800 nm. All NIR spectra were preprocessed using a default preprocessing of Savitsky-Golay smoothing (15 nm window, 2nd order polynomial) with 2nd derivative followed by magnitude upscaling by multiplication with a constant factor of 1000 and truncation of 50 nm from both ends of the spectra. All preprocessing treatments were completed in Python using the *SciPy* dependency or custom functions. The preprocessed and scaled pure component spectra are presented in **Figure 3**, except for Excipient E which did not have an available pure component spectrum.

Figure 2 *Image of a SentroPAT BU II – dedicated high performance NIR spectrometer PAT system*

Figure 3 *The pure component spectra after the default preprocessing and scaled to improve visualization.*



IOT ALGORITHM

$$\min_{r}(e^T e)$$

$$e = s^{mix} - s^{sim} = s^{mix} - rK$$

$$Constraints: \sum r = \alpha \ \ and \ \ \beta \leq r_k \leq \gamma$$

Variable Key

- s^{mix} = Experimental mixture spectrum
- s^{sim} = Simulated mixture spectrum
- e = Residuals
- K = Pure component spectra
- r = Relative contributions/concentrations

MB F-TEST RESULTS

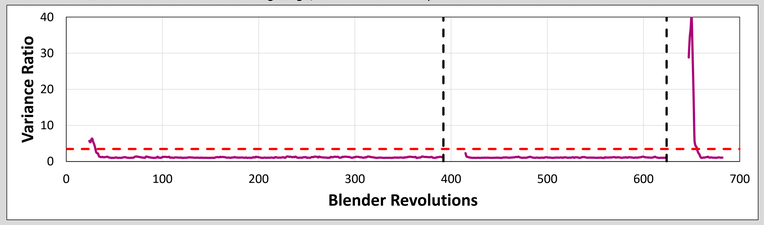
***Technique*:** MB F-test

Software: Python via custom functions, also available in ***SentroSuite***

Parameterization: Block size of 12 spectra

Discussion: The MB F-test trend (**Figure 4**) is only a summary of the blending process as observed by the NIR spectrometer, making it difficult to develop process understanding around specific events in the trend. For example, it is not descriptive of the chemical blending dynamics around the curve trends at the beginning of the main blend and lubrication stages. The stabilization of the MB F-test by the end of the lubrication stage below the critical F value ($\alpha = 0.05$) suggests that BU was achieved.

Figure 4 *The MB F-test for the NIR spectra collected with the SentroPAT BU II of the bin blending process. The black lines indicate the division between each blending stage, and the red line represents the critical F value at $\alpha = 0.05$*



PCA RESULTS

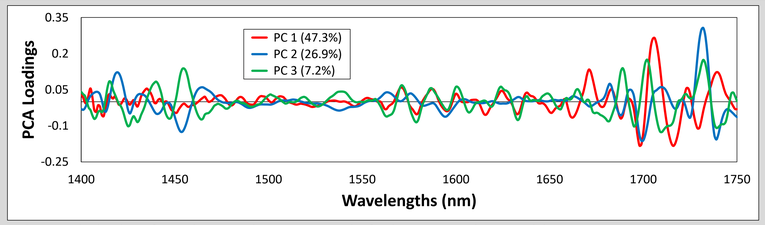


Figure 5 *The loadings for each principal component in the final unsupervised PCA model.*

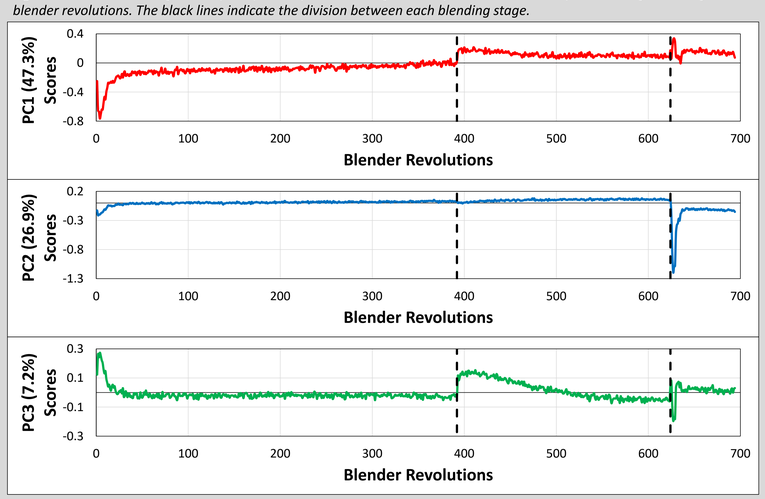
Technique: Unsupervised PCA

Software: Python via *SciPy* and custom functions

Parameterization: 3 principal components (PCs)

Discussion: Comparing the loadings (**Figure 5**) to the preprocessed pure component spectra, it is challenging to definitively identify any given loading with an individual chemical component. For example, PC 1 appears to capture information about the API, Excipient B, and Excipient D simultaneously. This makes it difficult to determine what information about the process the score trends are capturing (**Figure 6**)**.** To summarize the scores as a single trend, the distance between the scores of a single sample and a "golden batch" dataset could be calculated. However, acquiring the golden batch dataset increases the calibration burden. The stabilization of the scores by the end of the lubrication stage suggests that BU was achieved.

Figure 6 *The score trends for each principal component in the final unsupervised PCA model plotted as a function of blender revolutions. The black lines indicate the division between each blending stage.*



IOT RESULTS

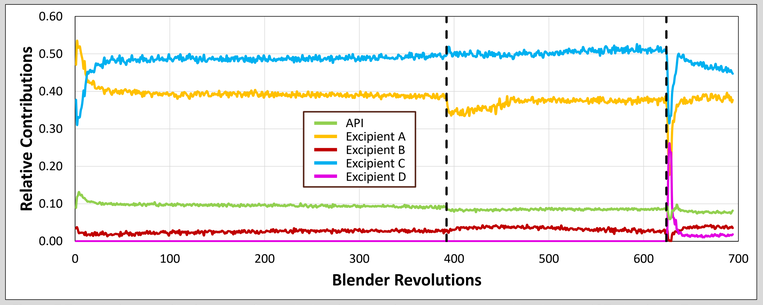


Figure 7 *The relative contribution trend for each chemical constituent, as calculated by the base IOT algorithm. The black lines indicate the division between each blending stage.*

Technique: Base IOT

Software: Python via custom functions using the OSQP solver, coming soon to ***SentroSuite***

Parameterization: Constraints of $\sum r \leq 100\%$ and $0 \leq r_k \leq 1$

Discussion: The relative contributions (**Figure 7**) offer more interpretable trends compared to the PCA scores, as each trend is directly related to an individual chemical constituent. The screening step before the main blend stage breaks down agglomerates formed in the pre-blend stage, requiring additional blending as seen in the relative contribution trends. The spike observed at the beginning of the lubrication stage in the MB F-test analysis is directly a result of Excipient D addition, information otherwise unattainable without *a priori* knowledge. The rank ordering of the relative contributions at the end of the lubrication stage show agreement with the target formulation constituent concentrations.

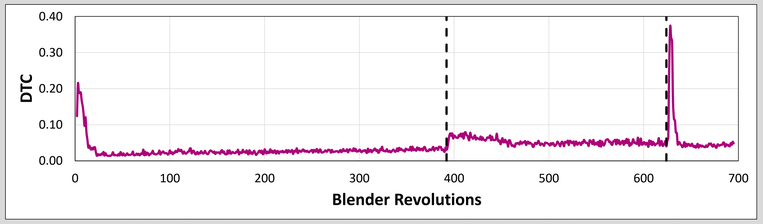


Figure 8 *The DTC (calculated from the IOT relative contributions and target formulation) for the NIR spectra collected with the SentroPAT BU II of the bin blending process. The black lines indicate the division between each blending stage.*

Rather than relying on MB F-test as a qualitative summary trend, the concept of *distance to target concentration* (DTC) is introduced to summarize the IOT relative contribution trends. This qualitative metric calculates the L2 (Euclidean) distance between the relative contributions and the nominal target formulation at each blender revolution (**Figure 8**) and is related to the quantitative metric *root mean square error from the nominal value* (RMSNV). The DTC approach notably does not require parameter optimization like the MB F-test. The DTC trend shows good agreement with the MB F-test and PCA score trends, suggesting that BU was achieved when the DTC trend stabilizes at the end of the lubrication stage.

SUMMARY

- The blending dynamics of a pharmaceutical formulation was monitored across all bin-blending stages using NIR spectroscopy via the SentroPAT BU II. The following chemometric techniques were used for qualitative assessment: MB F-test, unsupervised PCA, and IOT.
- The IOT offered enhanced interpretability over the unsupervised PCA by providing individual trends for each chemical constituent, rather than as combinations of constituents captured by the loadings.
- The DTC trend derived from the IOT relative contributions enabled a summary metric trend of the NIR spectroscopy data comparable to the MB F-test trend, but provided more details to enhance process understanding.
- These results suggest that IOT algorithm with DTC is a viable lean chemometric technique for qualitative BU analysis, providing easy to interpret trends about the blending process.

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