Evaluation of Near Infrared (NIR) for the Qualitative Detection of Low Dose Drugs

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Abstract

Qualitative models based on near infrared (NIR) offline data were successfully developed to monitor drug blends falling within or outside of ± 15% of 3% w/w acetaminophen concentration with 93.3% accuracy, 94.9% precision, 94.9% sensitivity, and 90.2% specificity. Excipient quality control models were also developed with 100% classification accuracy.

Research Background

FDA has approved NIR to monitor low- and medium-risk drug products, having already approved eight solid oral drug products for continuous manufacturing. However, as an emerging technology, NIR-based chemometric models have not been validated for in-process measurements for low dose, high-risk drug products. Since the powder blending process is essential for manufacturing solid oral dosage forms, this project examined the suitability of NIR as a process analytical technology (PAT) tool to accurately monitor 3% w/w acetaminophen blends falling within or outside of specifications. Qualitative models were developed based on NIR offline spectra of drug blends. The developed models were able to rapidly screen out-of-specification drug blend samples. Quality controls for the raw materials used for preparing powder blends, as well as controls for particle size distribution, were also integrated into the development of the qualitative NIR-chemometric model.

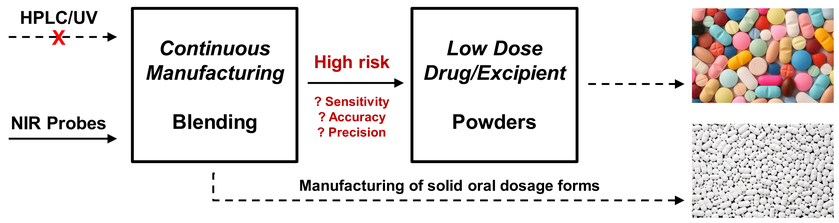


Figure 1. Graphical representation of the motivation behind investigating NIR for detection of low dose drugs.

Method

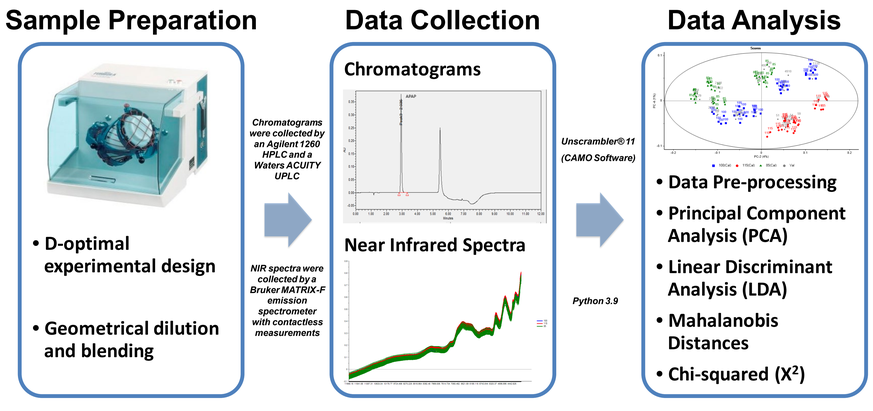


Figure 2. Sample preparation, data collection, and data analysis methods employed. Powder blends were prepared via tumble mixing. API content for blends was assessed via HPLC/UPLC. NIR spectra were measured for all samples. Raw material identification models and the blend qualitative model were developed using a combination of PCA and LDA.

Results and Discussion

- The critical Chi-square (χ^2) value of 101 training samples' Mahalanobis distances at the 90% confidence interval was computed as a model specificity cutoff threshold. The model specificity was established to ensure that excipients or chemically similar drugs did not interfere with the ability of the model to identify the API of interest. Specificity tests showed that placeboes or other API blends did not interfere the model capability to identify the API of interest within acceptable drug concentration range (Figure 3).
- Two critical χ^2 values of 101 training samples' Mahalanobis distances at the 10% and 15% significance levels served as a qualitative model for unknown sample identification. 33 internal validation samples were used to validate the model. The samples located between the 85% confidence interval and 90% confidence interval were flagged for further review and temporarily treated as failure samples. The samples located below the cutoff χ^2 value at the 85% confidence interval were identified as passing samples, whose drug concentration level was between 85% and 115%. Through 119 external validation samples, the model demonstrated 93.3% accuracy, 94.9% precision, 94.9% sensitivity, and 90.2% specificity (Figure 4).
- NIR LDA models for the identification of API and excipients were developed and validated. All raw materials were predicted with 100% accuracy (Figure 5). NIR PCA projection and LDA classification models were also developed to control the MCC and MgSt qualities from different vendors with 100% accuracy (Figure 6 and Figure 7). No model is needed for differentiating APAP sources since the USP monograph for APAP is sufficient to control consistent chemical attributes of the API regardless of manufacturers.

Specificity Test Results

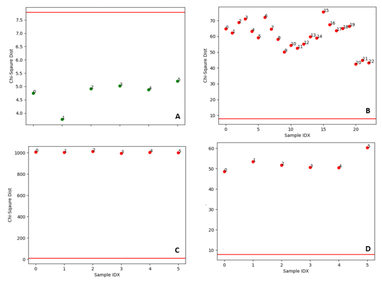


Figure 3. A: 115% CL APAP blends, B: Four placebo formulations, C: 0.67% molecule A blends, D: 3.0% molecule A blends (Green: API samples, Red: Non-API Samples, Red line: 90% CI).

External Validation Results of the Qualitative Model

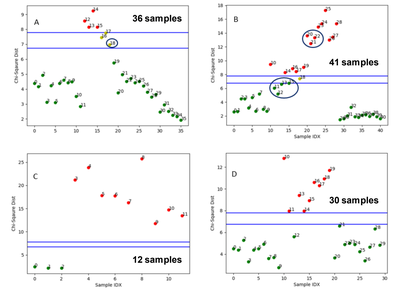


Figure 4. Upper blue line: 90% CI, Lower blue line: 85% CI. Green: Pass, Red: Fail. Circled samples were misclassified.

Raw Material Identification Prediction Accuracy Rate

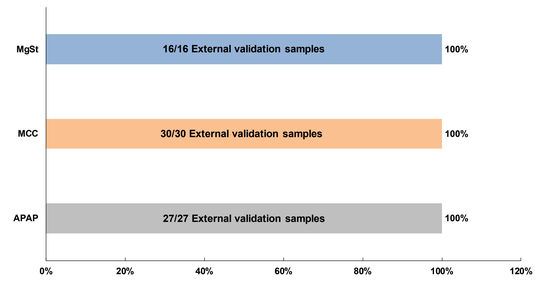


Figure 5. Raw material identification prediction accuracy rate.

Figure 6. MCC source qualification prediction accuracy rate.

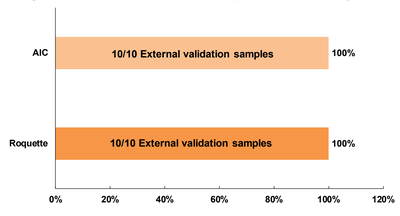
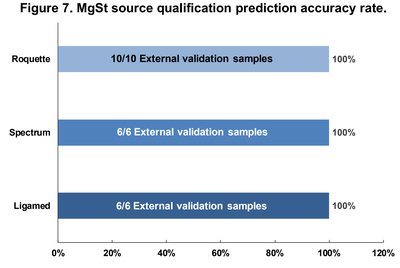


Figure 7. MgSt source qualification prediction accuracy rate.



Conclusions

- NIR LDA models were successfully developed to qualify the properties of the raw materials used to prepare low dose APAP blends.
- NIR model specificity was successfully used to identify whether a sample contains the API of interest.
- Critical Mahalanobis distance Chi-square values were used as a successful qualitative model to identify out-of-specification powder blend samples with a target content of 3.0% w/w APAP. This control method may be suitable in multiple continuous manufacturing processes.

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Disclaimer

This poster reflects the views of the authors and should not be construed to represent FDA's views or policies.