Chemical and biological sensors

Quantitative Detection of Naproxen Surface Residue Using FTIR Spectroscopy and Partial Least Squares Regression

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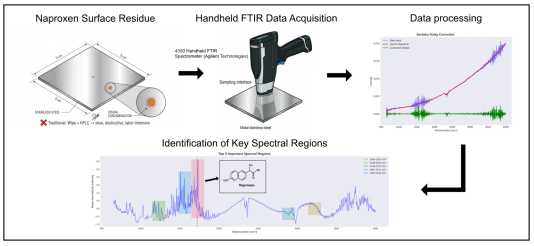
Abstract—Cleaning validation is essential in pharmaceutical manufacturing to prevent cross-contamination, yet traditional wipe-sampling and chromatographic methods are labor-intensive and time-consuming. This study demonstrates handheld Fourier transform infrared (FTIR) spectroscopy combined with partial least squares (PLS) regression as a rapid, nondestructive alternative for quantifying naproxen surface residue on stainless steel. A total of 293 FTIR spectra were collected from stainless steel coupons spiked with naproxen (0 to 5.15 μg cm^{-2}) over 650 cm^{-1}–4000 cm^{-1}. After outlier removal (IQR method), 263 spectra were retained and preprocessed using Savitzky–Golay smoothing and standard normal variate (SNV) normalization. The global PLS model (fivefold CV) achieved $R^2 = 0.854$, RMSE = 0.491 μg cm^{-2}, limit of detection (LOD) = 1.95 μg cm^{-2}, and limit of quantification (LOQ)= 5.92 μg cm^{-2}. Interval PLS identified the 1646–1810 cm^{-1} region (naproxen C = O stretch) as most predictive, yielding markedly improved performance: $R^2 = 0.973$, RMSE = 0.211 μg cm^{-2}, LOD = 0.716 μg cm^{-2}, and LOQ = 2.169 μg cm^{-2}. These results demonstrate that chemometric interval selection substantially enhances sensitivity and chemical interpretability, establishing handheld FTIR-interval partial least squares as an efficient, nondestructive alternative for routine pharmaceutical cleaning verification.



Index Terms—Chemical and biological sensors, chemometrics, cleaning validation, Fourier transform infrared (FTIR) spectroscopy, naproxen, partial least squares (PLS) regression, surface residue.

I. INTRODUCTION

Pharmaceutical manufacturing requires rigorous cleaning validation to prevent cross-contamination and ensure product safety [1]. Traditional methods, such as wipe-sampling followed by high-performance liquid chromatography (HPLC), are effective but labor-intensive, destructive, and slow [2]. Fourier transform infrared (FTIR) spectroscopy offers a promising alternative, providing rapid, nondestructive analysis through molecular fingerprinting [3]. When combined with chemometric techniques, such as partial least squares (PLS) regression, FTIR can quantify contaminants with high precision [4].

Prior studies have applied FTIR spectroscopy for the detection of pharmaceutical surface residues [5]. Nevertheless, traditional wipe-sampling followed by HPLC remains the dominant approach for cleaning verification, even as industry trends have increasingly focused on refining residue limits to ensure safety [6]. Recent advances in handheld FTIR spectroscopy have positioned it as a rapid, nondestructive alternative. Sarwar et al. [2] and [5] developed quantitative PLS regression models for pharmaceutical surface residues and investigated practical aspects, such as the number of scans required and the effect of surface roughness. Jul-Jørgensen et al. [8] showed that handheld FTIR with PLS-DA can outperform or match total organic carbon swab sampling for binary "clean/not clean" decisions. However, published quantitative regression models across a continuous concentration range remain limited for many specific active pharmaceutical ingredients, such as naproxen, and the potential of *interval partial least squares (iPLS)* has not yet been explored in the context of handheld specular reflectance FTIR for pharmaceutical cleaning verification on stainless steel surfaces.

This study addresses these gaps by developing a quantitative handheld specular-reflectance FTIR-PLS model for naproxen surface residues (0–5.15 μg cm^{-2}) on stainless-steel coupons representative of manufacturing equipment. Interval PLS was applied to isolate the dominant naproxen C=O stretching region (1646–1810 cm^{-1}), yielding substantially improved sensitivity and chemical interpretability compared with the global model. Performance was evaluated using fivefold cross-validation, and key analytical figures of merit (R^2, RMSE, LOD, and LOQ) were determined. To the best of the authors' knowledge, this represents the first detailed quantitative iPLS-based approach for naproxen residue detection using handheld specular reflectance FTIR on stainless steel.

II. MATERIALS AND METHODS

A. Dataset Acquisition and Quality Control

FTIR spectra were acquired using a 4300 Handheld FTIR Spectrometer (Agilent Technologies) equipped with a specular external

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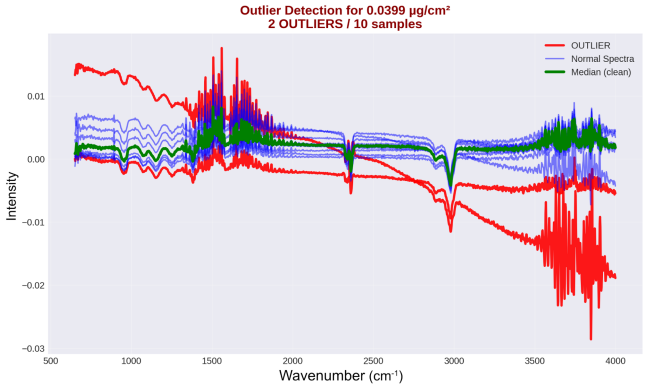

Fig. 1. Visualization of outlier detection using the IQR method.

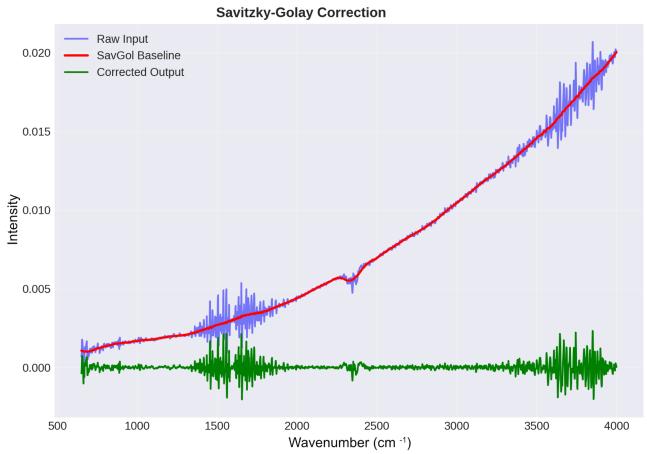

Fig. 2. Effect of Savitzky–Golay baseline correction.

TABLE 1. Performance Metrics of the Global PLS Model

Metric	Value
Slope (S)	0.7960
Sigma (σ residuals)	0.4839 μg cm^{-2}
LOD (3.3σ/S)	1.95 μg cm^{-2}
LOQ (10σ/S)	5.92 μg cm^{-2}
R^2 (Five-fold CV)	0.8542
RMSE	0.491 μg cm^{-2}

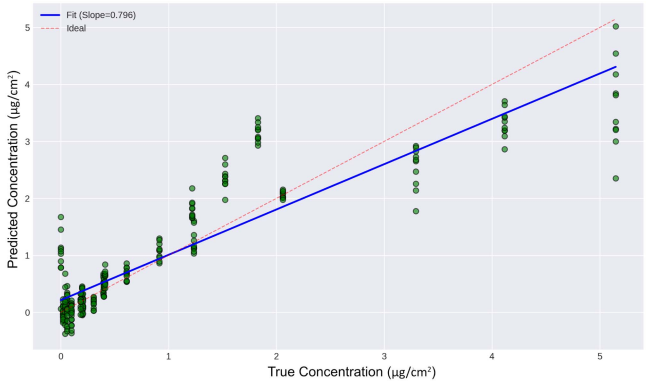

Fig. 3. Global model predictions. Predicted versus true concentrations.

reflectance sample interface. Stainless steel coupons (5 cm × 5 cm, surface finish #8; PhotonSystems Inc.) served as substrates. The identical #8 mirror finish on all coupons minimized intersample spectral variation due to surface roughness and shininess.

Naproxen (Orion Pharma) was dissolved in ethanol (99.8 %, Anora Group) and printed using a ChemCal Printer 5.0 (PhotonSystems Inc.). The printer dispensed 256 droplets (10.55 nl each) over a 15 mm × 15 mm area (1 mm spacing, Interleave setting enabled), yielding uniform surface concentrations from 0μg cm^{-2} to 5.15 μg cm^{-2}. Coupons were dried at room temperature until the solvent fully evaporated.

Spectra were recorded over 650 cm^{-1}–4000 cm^{-1} at 4 cm^{-1} resolution with 40 background and 40 sample scans (Happ-Genzel apodization). The spectrometer was mounted on an operating stand facing downward. Each coupon was positioned so that the built-in O-ring of the specular external reflectance interface gently contacted the surface, fixing the focal distance and maintaining a constant 45° incidence angle. A new background spectrum was taken from a clean coupon of the same finish before each sample. Ten replicate measurements per coupon with slight positional adjustments yielded a total of 293 spectra.

Outliers (30 spectra, 10.2 %) were removed using the interquartile-range method on principal component scores [9], resulting in 263 retained spectra (see Fig. 1).

B. Data Preprocessing

Raw spectra were preprocessed using Python 3.9 with the scikit-learn library (version 1.0.2) and SciPy (version 1.7.3). Baseline correction was performed via Savitzky–Golay smoothing (window length 51, polynomial order 2), with parameters selected via systematic grid search to minimise the root-mean-square error of the baseline-corrected spectra while preserving the integrity of analytical peaks (see Fig. 2) [10]. Subsequently, SNV normalization was applied to correct for intensity variations and scattering artefacts common in reflectance spectroscopy [11].

C. Modeling Strategy

A global PLS regression model was built using scikit-learn's PLS regression module with fivefold cross-validation. The optimal number of latent variables (eight for the global model and seven for the interval model) was selected via grid search to minimise the cross-validation RMSE. PLS regression is a multivariate statistical method that projects predictors and responses into a latent space to maximise covariance while handling multicollinearity in high-dimensional spectral data [4] and [7]. Interval PLS was employed to identify the most important spectral regions corresponding to naproxen-specific peaks. The spectrum was divided into 20 equidistant intervals and independent PLS models were built for each to determine the regions with the highest predictive power [12]. The performance of the best interval was compared with the global model.

III. RESULTS

A. Global Model Performance

The global PLS model exhibited reasonable predictive performance, achieving an R^2 (fivefold CV) of 0.854 and an RMSE of 0.491 μg cm^{-2}

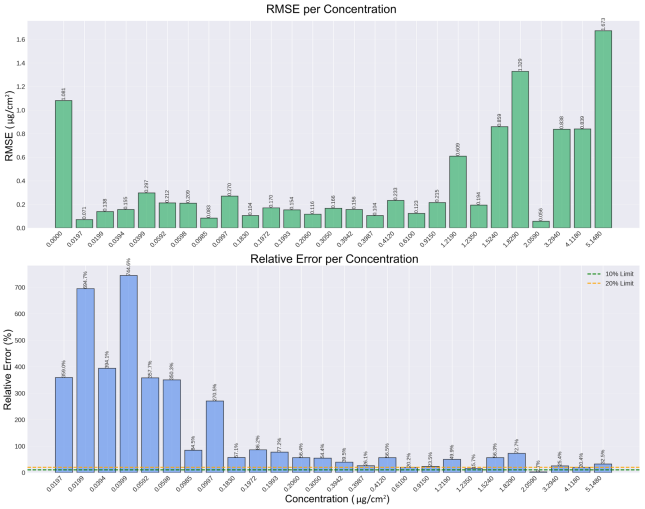

Fig. 4. RMSE (top) and relative error (bottom) per concentration level for the Global PLS Model.

TABLE 2. Top 5 Spectral Intervals Contributing to Prediction Accuracy

Rank	Range (cm^{-1})	Key Feature
1	1646–1810	Naproxen C=O stretch
2	3138–3302	O–H stretch
3	1148–1312	C–O stretch
4	2807–2971	C–H stretch
5	1480–1644	Aromatic ring modes

TABLE 3. Performance Metrics for the Most Important Interval (1646–1810 cm^{-1})

Metric	Value
Slope (S)	0.9860
Sigma (σ residuals)	0.2103 $\mu g\,cm^{-2}$
LOD (3.3σ/S)	0.716 $\mu g\,cm^{-2}$
LOQ (10σ/S)	2.169 $\mu g\,cm^{-2}$
R^2 (5-fold CV)	0.9729
RMSE	0.211 $\mu g\,cm^{-2}$

(see Table 1). Fig. 3 shows the predicted versus reference concentrations across the full calibration range (0 to 5.15 $\mu g\ cm^{-2}$), with a linear relationship (slope = 0.796 and $R^2 = 0.8542$) and moderate scatter above 2 $\mu g\ cm^{-2}$. Concentration-dependent error profiles are presented in Fig. 4.

B. Identification of Key Spectral Regions

The preprocessed spectral data were divided into 20 equidistant intervals. Independent PLS models were built for each interval to identify regions with the strongest predictive correlation to naproxen concentration, quantified by the cross-validated coefficient of determination (R^2_{CV}). The most predictive interval (1646–1810 cm^{-1}) achieved an R^2 (fivefold CV) of 0.973 and an RMSE of 0.211 $\mu g\ cm^{-2}$. The ranking of all five intervals by predictive accuracy is summarized in Table 2. Performance metrics for this interval are given in Table 3. The interval PLS model exhibited clear linearity between predicted and reference concentrations (slope = 0.9860 and $R^2 = 0.9729$) with only

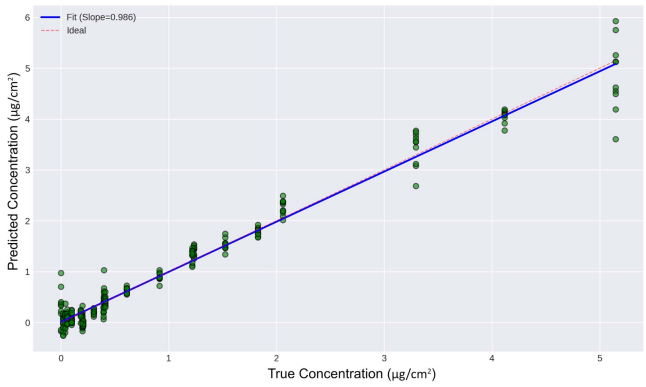

Fig. 5. Interval model predictions (1646–1810 cm^{-1}): Predicted versus true concentrations.

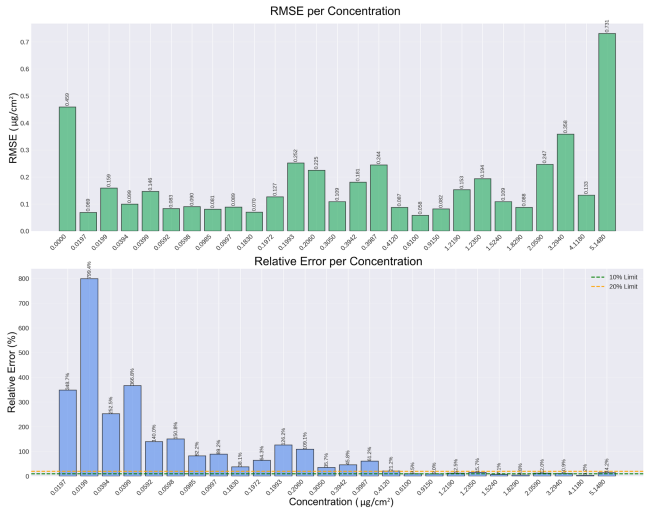

Fig. 6. RMSE (top) and relative error (bottom) per concentration level for the Interval PLS Model (1646–1810 cm^{-1}).

minor scatter (see Fig. 5). Concentration-dependent error profiles are shown in Fig. 6.

IV. DISCUSSION

The combination of Savitzky–Golay baseline correction and SNV normalization enabled a global PLS model with solid predictive performance ($R^2 = 0.854$ and RMSE = 0.491 $\mu g\ cm^{-2}$) across the full calibration range (0–5.15 $\mu g\ cm^{-2}$). The derived limit of detection (LOD) and limit of quantification (LOQ) were 1.95 $\mu g\ cm^{-2}$ and 5.92 $\mu g\ cm^{-2}$, respectively. Although these values confirm the method's capability within the studied range, the relatively high LOQ indicates limited sensitivity for the trace-level residues typically required in pharmaceutical cleaning validation.

Interval PLS markedly improved model performance by isolating the most informative spectral region (1646–1810 cm^{-1}), corresponding to the carboxylic acid C=O stretching vibration of naproxen. While this band typically appears near 1729 cm^{-1} in pure naproxen, a red-shift (to lower wavenumbers) is observed on stainless steel due to hydrogen bonding and/or coordination of the carboxylate group with the surface oxide layer [13]. The iPLS model yielded substantially superior metrics ($R^2 = 0.973$, RMSE = 0.211 $\mu g\ cm^{-2}$, LOD = 0.716 $\mu g\ cm^{-2}$, and LOQ = 2.169 $\mu g\ cm^{-2}$), representing

nearly a threefold improvement in sensitivity. A traditional univariate calibration based on peak height and on integrated band area within the same C = O stretching region (1646–1810 cm^{-1}) both produced poor predictive performance (peak height: $R^2 = 0.1107$ and RMSE = 1.234 $\mu g\ cm^{-2}$; integrated band area: $R^2 = 0.2032$ and RMSE = 1.168 $\mu g\ cm^{-2}$). These results highlight the limitations of conventional univariate approaches, which are particularly susceptible to baseline fluctuations and scattering effects inherent in handheld specular reflectance FTIR measurements on stainless steel surfaces.

Concentration-dependent error profiles further confirmed the superiority of the interval model, particularly at low concentrations relevant to cleaning validation. Surface-related artefacts inherent to specular reflectance FTIR were effectively mitigated by using identical #8 mirror-finish stainless steel coupons and the O-ring-equipped interface, which ensures a reproducible focal distance and fixed 45° incidence angle; SNV normalization provided additional correction for multiplicative scatter.

For regulatory acceptance and routine implementation, a complete analytical method validation according to USP General Chapters ⟨1039⟩ [14] (Chemometrics) and ⟨1225⟩ [15] (Validation of Compendial Procedures) is required, including selectivity, intermediate precision, and robustness. The present study focused on model development and internal cross-validation. Compared with conventional wipe-sampling followed by HPLC [2], the FTIR-iPLS approach offers significant practical advantages, including rapid, nondestructive, on-surface measurement with minimal sample preparation and enhanced chemical interpretability. Future work will address full validation, advanced preprocessing techniques, and direct evaluation on real manufacturing equipment surfaces (e.g., tablet-press tooling) to support routine cleaning verification in multiproduct facilities.

V. CONCLUSION

This study demonstrates that handheld FTIR spectroscopy combined with iPLS regression provides a rapid, nondestructive, and sensitive method for quantifying naproxen surface residue on stainless steel. Targeted selection of the characteristic carbonyl stretching region markedly increases sensitivity and predictive accuracy at trace levels, making FTIR-iPLS well-suited for stringent cleaning validation requirements in pharmaceutical manufacturing and a practical alternative to conventional wipe-sampling and HPLC-based methods.

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