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Physics-Informed Neural Networks for NIR Spectroscopy Analysis of Pharmaceutical Tablet Properties

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ABSTRACT

In pharmaceutical process engineering, accurate prediction of tablet properties is crucial for ensuring product quality, optimizing manufacturing efficiency, and advancing sustainable production practices. This study presents a physics-informed neural network (PINN) framework for predicting the physical properties of pharmaceutical tablets from near-infrared (NIR) spectra. The PINN framework integrates revised Kubelka-Munk theory and physical constraints to ensure physically consistent predictions while requiring less training data than conventional artificial neural networks. Tablets were manufactured using acetaminophen and microcrystalline cellulose formulations with varying compositions and compression settings. The PINN framework successfully predicts critical quality attributes, including tensile strength, porosity, and density. It offers a data-efficient, interpretable solution for pharmaceutical tablet quality control.

Keywords: Physics-Informed Neural Networks, Machine Learning, Industry 4.0, Near Infrared Spectroscopy, Pharmaceutical Tablets.

INTRODUCTION

Tablet quality attributes including size, hardness, tensile strength, porosity and density are critical for ensuring mechanical integrity, dissolution performance and bioavailability in pharmaceutical manufacturing [1,2]. The US Food and Drug Administration (FDA) requires rigorous monitoring of these properties as critical quality. However, different tablet compression machines, operating conditions and formulation compositions can introduce substantial quality variations. Traditional tablet testing methods are time consuming and destructive and only provides limited inspection into the sampled tablets.

Near-infrared (NIR) spectroscopy enables rapid, non-destructive and continuous analysis of tablets, which is suitable for process monitoring [3, 4]. Current NIR calibration methods employ chemometric techniques such as partial least squares regression (PLSR) or machine learning models like artificial neural networks (ANNs). However, in predicting physical properties, PLS models often struggles with accuracy, and ANNs requires substantial training datasets and offer limited model interpretability [5, 6].

The NIR reflectance of tablets is fundamentally governed by light scattering and absorption in porous media. The revised Kubelka-Munk theory (RKM), developed by Yang and Kruse, describes scattering-induced photon path variation (SIPV) to the original Kubelka-Munk theory. By introducing the SIPV factor μ, the RKM theory accounts for changes in the effective light path length in highly scattering samples [7]. This provides a physics-based framework for relating spectral features to tablet microstructure. Physics-informed neural networks (PINNs) integrate physical laws into the training process of neural networks, which can improve data efficiency and prediction consistency [8].

In this study, we present a PINN model that incorporates RKM equations to predict tablet properties based on NIR spectra. The model learns the intrinsic absorption and scattering coefficients, as well as the SIPV factor, while predicting tablet critical quality attributes. We compare the performance of the PINN-RKM model with conventional ANN model and evaluate the data requirements for both approaches. The results show that integrating physical constraints reduces the need for training data while maintaining prediction accuracy.

METHODS

Experiments

A powder formulation was prepared for the tablet production: 80% microcrystalline cellulose (Avicel PH-102, IFF, USA) and 20% acetaminophen (Mallinckrodt Pharmaceuticals). The powders were blended for 30 minutes in a five-liter tote blender and then processed through an Alexanderwerk WP120 roller compactor to produce granules. Ten granulation sets were produced for each formulation with varying roller compaction settings (roller speed, hydraulic pressure, and roll gap), while three granulation sets were further used to evaluate the proposed models.

Tablets were manufactured using a Natoli NP-400 tablet press with D-type tooling (D = 7.94 mm, h = 0.3302 mm) at a constant turret speed of 20 rpm, feed-frame speed of 35 rpm and precompression thickness of 6mm. Three main compression thickness settings (3.0, 3.5, and 4.5 mm) were used for each granule set.

Data Acquisition

For each tableting condition, 20 tablets were sampled and measured sequentially. Each tablet was measured three times. Near-infrared (NIR) reflectance spectra (1100–2100 nm) were acquired at-line with the probe in direct contact with the tablet surfaces. External referencing was performed before each dataset using a certified 99% reflectance Spectralon standard. An example of raw tablet spectra is shown in Figure 1. After the NIR measurement, the tablets were characterized using an AT4 tablet tester to determine their weight, hardness, diameter, and thickness. Tensile strength was calculated from the hardness measurements using the method described in Bachawala et al [].

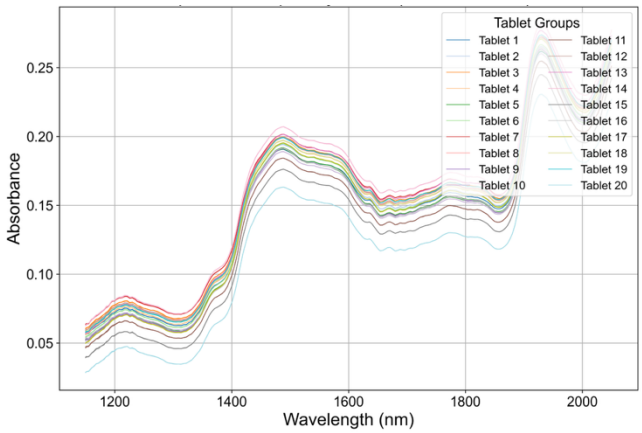

Figure 1. Raw NIR spectra from one tableting conditon.

Model Architecture

The revised Kubelka-Munk (RKM) theory describes effective absorption and scattering coefficients by $K = \mu * \alpha * a$ and $S = \frac{1}{2} * \mu * \alpha * s$, where a and s are the intrinsic absorption and scattering coefficients. α is the diffuse light factor, and $\mu = \sqrt{s/a}$ is the SIPV factor that characterizes the effective photon path length. The reflectance for an infinitely thick sample is $R_\infty = 1 + \left(\frac{K}{S}\right) - \sqrt{(K/S)^2 + 2(K/S)}$. This theory links NIR reflectance to tablet physical properties through the intrinsic optical coefficients.

The RKM theory describes light propagation in pharmaceutical tablets more accurately than the original Kubelka-Munk theory because it explicitly accounts for path variation. When photons scatter through an opaque and heterogeneous media, they do not follow straight paths. Instead, photons go through multiple scattering events, leading to path length distributions that deviate from the classical two-flux assumptions in original KM theory. The SIPV factor μ captures this phenomenon. When scattering dominates ($s > a$), photons travel longer effective distances ($\mu > 1$). This makes the RKM theory ideal for PINN implementations because it provides a mechanistic link between measurable NIR spectra and the underlying tablet microstructure. Therefore, the PINN can learn physically consistent representations of tablet properties rather than purely empirical correlations.

The PINN-RKM architecture we developed consists of multiple sub-networks that simultaneously predict tablet physical properties and optical coefficients from NIR spectra. Physics parameter networks predict porosity, density, and tablet thickness. A composition network estimates component fractions at absorption bands identified through SHapley Additive Explanations (SHAP) analysis of wavelength importance, which revealed key bands around 1150, 1450, 1730, 1940, and 2050 nm corresponding to characteristic chemical bonds in the formulation. Optical coefficient networks predict wavelength-dependent intrinsic coefficients a and s, which are then used to calculate the SIPV factor. A property prediction network maps the predicted physics parameters to target tablet properties.

The total loss function integrates data-driven and physics-informed terms: $\mathcal{L}_{total} = \mathcal{L}_{porperty} + w_1 * \mathcal{L}_{spectrum} + w_2 * \mathcal{L}_{physics} + w_1 * \mathcal{L}_{bounds}$, where $\mathcal{L}_{porperty}$ is the mean squared error between predicted and measured tablet properties, $\mathcal{L}_{spectrum}$ quantifies reconstruction error between measured and RKM predicted reflectance spectra, $\mathcal{L}_{physics}$ penalizes violations of physical constraints, and $\mathcal{L}_{bounds}$ enforces physically reasonable parameter ranges. Physical constraints include the porosity-density relationship, SIPV factor, and parameter bounds for porosity, density, intrinsic absorption coefficient, intrinsic scattering coefficient, thickness and light penetration depth. The constraint weights were empirically tuned to balance prediction accuracy and physical consistency.

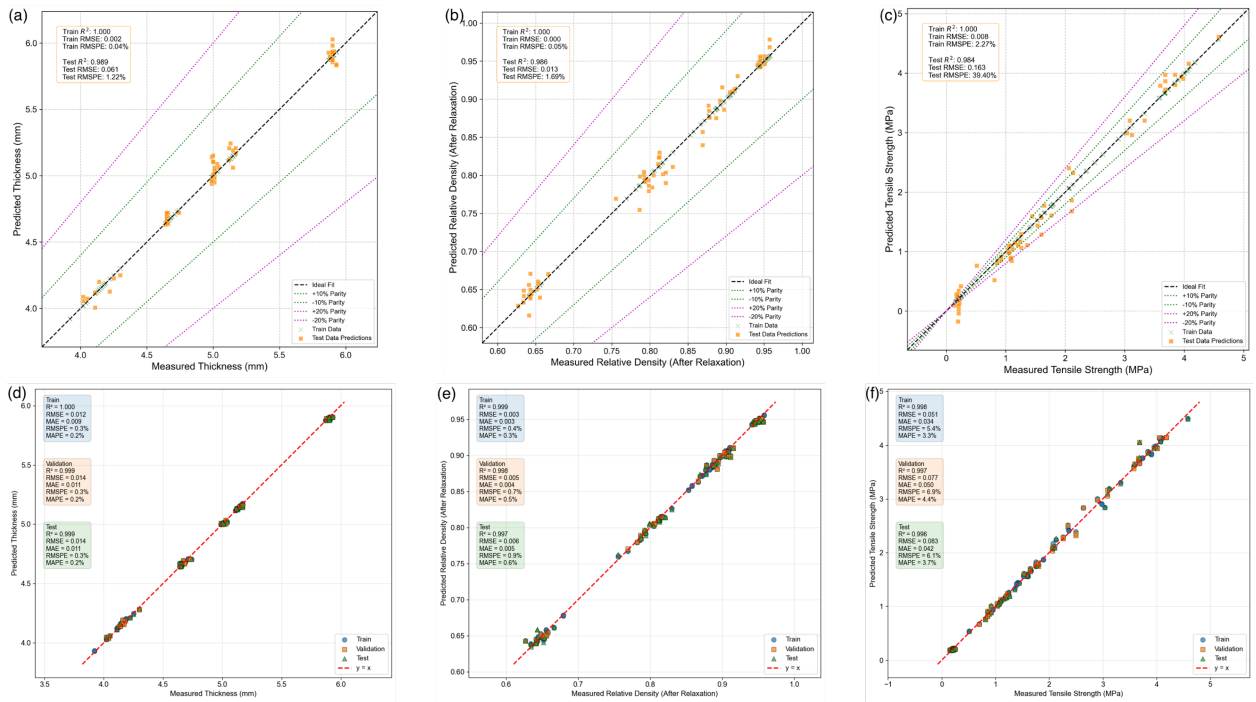

Figure 2. Parity plots of the ANN models (a) tensile strength (b) relative density (c) thickness, and PINN-RKM models (d) tensile strength (e)) relative density (f) thickness.

The network was implemented in PyTorch and trained using the Adam optimizer with learning rate 5×10-4 for 1500 epochs with early stopping (patience = 300 epochs). Data were split 70/30 for training and testing, with standard scaling applied to both NIR spectra and tablet properties. The PINN performance was evaluated against a conventional feedforward ANN with identical network capacity.

RESULTS AND DISCUSSION

Table 1 compares the performance of the proposed a PINN-RKM model with that of a standard ANN in predicting three critical tablet properties from near-infrared (NIR) spectra. The PINN-RKM model demonstrated higher predictive accuracy for all three tablet properties compared to the standard ANN approach. As shown in Figure 2, both models achieved high R^2 values, indicating strong correlations between predictions and reference values. However, the PINN-RKM model has substantially lower prediction errors. PINN-RKM model was able to achieve an improvement in tensile strength predictions, where it reduced the root mean square error (RMSE) by 49% (from 0.163 to 0.083) compared to the standard ANN model. For relative density and thickness predictions, the PINN-RKM model achieved reductions in RMSE of 54% and 77%, respectively. This demonstrates its consistent superiority across properties with different physical characteristics and measurement scales.

Table 1: Modeling results.

Model	TestR^2	RMSE	RMSPE(%)
Tensile Strength			
PINN-RKM	0.996	0.083	6.1
ANN	0.984	0.163	39.4
Relative Density			
PINN-RKM	0.997	0.006	0.9
ANN	0.986	0.013	1.69
Thickness			
PINN-RKM	0.999	0.014	0.3
ANN	0.989	0.061	1.22

Beyond improved accuracy, the PINN-RKM framework provides physically interpretable parameters that offer mechanistic insights into tablet microstructure and light-matter interactions. Figure 3 illustrates the wide range of physical properties and the correlations between the properties and the tablet tensile strength.

As shown in Figure 3, the tablet porosity ranged from 0.06 to 0.21 with a mean of 0.12, while the density distribution peaked at a mean of 1.2. These variations directly influenced the SIPV factor, which showed a mean value of 2.18. A clear positive correlation was observed between porosity and the SIPV factor. As porosity increases, the increased number of air-solid interfaces

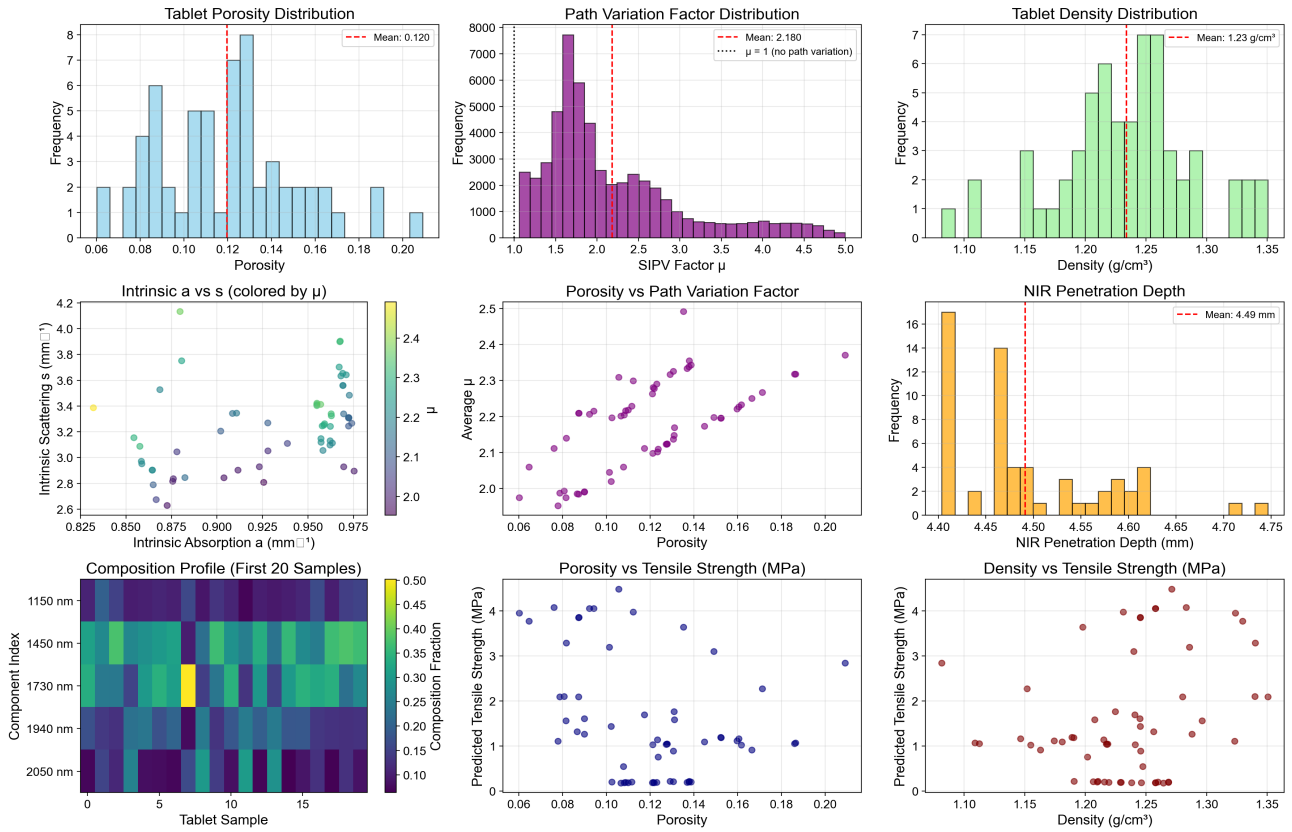

Figure 3. PINN-RKM model mechanistic interpretations.

within the tablet enhances light scattering, thereby extending the total photon pathlength. Furthermore, the NIR penetration depth aligns with the tablet thickness settings, suggesting that the NIR spectra effectively sampled the internal bulk properties of the tablets. However, previous research indicates that the NIR penetration depth in pharmaceutical compacts typically does not exceed 3 mm. Although our model results indicate effective sampling up to the maximum experimental thickness, this discrepancy highlights the need for further study to confirm the accuracy of depth predictions.

CONCLUSION

This research introduces a novel Physics-Informed Neural Network (PINN) architecture integrated with Revised Kubelka-Munk (RKM) theory for the non-destructive characterization of pharmaceutical tablets. By including fundamental light-propagation physics into the deep neural networks, the model successfully transitioned from a traditional empirical correlation to a robust, physics-aware predictive framework. The PINN-RKM model demonstrated superior predictive performance across all evaluated Critical Quality Attributes (CQAs). Specifically, the framework achieved an R2 of 0.999 for thickness and 0.998 for tensile strength, significantly outperforming conventional artificial neural. In summary, the integration of RKM physics provides a significant advancement. This method not only enhances predictive accuracy but also offers a high degree of model interpretability, providing a solid solution for process monitoring and quality assurance in pharmaceutical manufacturing.

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