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Near-infrared spectroscopy for rapid quality assessment of pharmaceutical tablets

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Abstract

Traditional destructive quality control methods for pharmaceutical tablets content uniformity by HPLC, hardness by physical testing, and dissolution by USP Apparatus II are time-consuming, reagent-intensive, and can only sample a small fraction of each batch. Near-Infrared (NIR) spectroscopy offers a compelling contrast: measurements take under 60 seconds, require no sample preparation, and are entirely non-destructive. In this research, a NIR reflectance method was developed and validated for the simultaneous prediction of Active Pharmaceutical Ingredient (API) content, tablet hardness, and weight variation in metformin hydrochloride tablets. Sixty tablet samples covering the intended calibration range (85-115% label claim for API; 60-120 N for hardness) were scanned on a Bruker Multi Purpose Analyser (MPA) FT-NIR spectrometer in the 4000-12000 cm^{-1} range. Spectra were pre-processed by Standard Normal Variate (SNV) transformation followed by second-derivative Savitzky-Golay smoothing. Partial least squares (PLS) regression models were developed using leave-one-out cross-validation and independently validated with a separate set of 30 tablets. The API content model achieved $R^2 = 0.9973$, RMSECV = 0.48%, and RMSEP = 0.62% label claim. The hardness model yielded $R^2 = 0.9841$ and RMSEP = 3.2 N. Weight variation prediction gave $R^2 = 0.9712$ and RMSEP = 2.1 mg. Prediction errors for API content fell within $\pm 1.5\%$ for 90% of validation samples. The validated NIR method meets the performance requirements for at-line quality control under ICH Q2(R1) and supports implementation as a Process Analytical Technology (PAT) tool under ICH Q8 and Q10 guidance.

Keywords: Near-infrared spectroscopy, pharmaceutical tablets, quality assessment, PLS calibration, PAT, content uniformity, NIR, rapid analysis

Introduction

Unlike UV-Vis or mid-infrared spectroscopy, NIR occupies a frequency region roughly 780 to 2500 nm that is, on the face of it, less information-rich: bands here arise from overtone and combination transitions rather than fundamental vibrations, making them broader and less structurally diagnostic. And yet it is precisely these features high photon penetration depth, minimal scattering effects with modern fibre-optic probes, and compatibility with solid samples that have made NIR the spectroscopic technique of choice for high-throughput pharmaceutical quality control ^[1]. Combined with multivariate chemometric models, NIR can extract quantitative predictions of multiple physical and chemical tablet attributes simultaneously from a single spectral measurement lasting less than a minute ^[2].

The pharmaceutical industry's shift toward Quality by Design (QbD) and Process Analytical Technology (PAT) frameworks, formalised in ICH Q8, Q9, and Q10 guidelines, has greatly accelerated NIR adoption in tablet manufacturing. PAT tools are expected to provide real-time or near-real-time information on Critical Quality Attributes (CQAs) during manufacturing, enabling in-process control decisions that reduce end-product testing burden and improve batch consistency ^[3]. NIR is well-positioned to fill this role for solid dosage forms because it can be deployed both at-line (benchtop analyser) and in-line (embedded probe in the compression machine), and because calibration models once validated can be transferred across instruments with appropriate standardisation procedures ^[4].

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Metformin hydrochloride, as the most widely prescribed oral antidiabetic medicine globally, is produced in extremely large batch volumes making even a modest improvement in QC throughput economically significant. Published NIR methods for metformin tablets exist but most were developed on specific proprietary instruments with limited transferability data, and few have addressed simultaneous prediction of physical parameters (hardness, weight) alongside chemical content [5, 6]. Additionally, validation of NIR pharmaceutical methods specifically against the ICH Q2(R1) framework for secondary methods including assessment of precision, accuracy, and linearity under the PLS prediction context remains inconsistently reported in the literature.

This research therefore aimed to develop and fully validate a NIR PLS method for metformin tablets covering API content, hardness, and weight variation simultaneously, with a view to implementation as a PAT tool. The work was carried out at the Department of Instrumental Analysis, Udayana Institute of Green Chemistry, Goa, India, between September 2023 and February 2025.

Instrumentation and analytical equipment

NIR spectra were acquired on a Bruker MPA FT-NIR spectrometer (Bruker Optik GmbH, Ettlingen, Germany) in diffuse reflectance mode using a tablet integrating sphere accessory. Spectral range: 4000-12000 cm^{-1} ; resolution: 8 cm^{-1} ; co-addition: 32 scans per spectrum. Instrument qualification was performed per USP <1119> guidance using NIST-traceable wavelength verification standards. Reference HPLC analysis for API content used an Agilent 1260 Infinity II system with a Phenomenex Synergi Polar-RP column (150 $\times$ 4.6 mm, 4 μm); mobile phase 0.1% TFA in water at 1.0 mL/min; detection at 232 nm. Tablet hardness was measured on an Erweka TBH 425 hardness tester (Erweka GmbH, Heusenstamm, Germany); results are in Newtons (N). Tablet weight variation was determined gravimetrically on a Mettler Toledo XSR205DU analytical balance (readability 0.01 mg). Chemometric modelling used OPUS 8.7 software (Bruker) with the integrated PLS module; cross-validation was leave-one-out for calibration and independent validation with a separate set. Temperature in the NIR laboratory was maintained at $22 \pm 2^\circ\text{C}$ and relative humidity at $45 \pm 5\%$ throughout all measurements.

Material and Methods

Material

All research was conducted at the Department of Instrumental Analysis, Udayana Institute of Green Chemistry, Goa, India, from September 2023 to February 2025. Metformin hydrochloride tablets (500 mg label claim, various commercial lots from three local generic manufacturers) were used as the calibration and validation set. Reference standard metformin hydrochloride (99.8%, EP grade) was sourced from Sigma-Aldrich (Bangalore, India). HPLC-grade acetonitrile and trifluoroacetic acid were from Rankem (Gurugram, India). Microcrystalline cellulose (Avicel PH-102), povidone K30, and magnesium

stearate were obtained from SD Fine Chemicals (Mumbai, India) and used for preparation of in-house spiked reference tablets spanning the calibration range. Tablets with API content of 85%, 90%, 95%, 100%, 105%, 110%, and 115% label claim were prepared by direct compression on a single-punch press (Cadmach CIP-D, Ahmedabad, India). The study design was approved by the Scientific Committee, Udayana Institute of Green Chemistry (Ref. UIGC-SC-2023-05, dated 6 September 2023); no human or animal subjects were involved.

Methods

Calibration set construction: Sixty tablets covering 85-115% API label claim (20 spiked + 40 commercial), 60-120 N hardness, and 480-520 mg weight were assembled. Each tablet was scanned by NIR, then analysed by HPLC for API content, hardness tester, and balance for weight. **Spectral pre-processing:** Raw reflectance spectra were converted to $\log(1/R)$, followed by SNV transformation to correct for scattering effects, then second-derivative smoothing (Savitzky-Golay, 11-point window, 2nd polynomial order) to resolve overlapping bands. **Spectral range selection:** The 4000-7500 cm^{-1} region was used for final models based on maximum loading weights; the region above 7500 cm^{-1} showed high noise contribution. **PLS model development:** Number of Latent Variables (LVs) was selected by minimum RMSECV using leave-one-out cross-validation; 8 LVs for API, 6 LVs for hardness, 5 LVs for weight. **Validation:** An independent set of 30 tablets (15 spiked + 15 commercial, not used in calibration) was measured and predicted; RMSEP and bias were calculated. **Method validation followed ICH Q2(R1) adapted for secondary PLS methods:** linearity by calibration range, precision by 10 replicate measurements of one tablet per day $\times$ 3 days, accuracy by recovery from spiked samples.

Quality control

Instrument performance was verified daily before measurements using certified NIST-traceable reflectance standards and a wavelength verification standard (Spectralon NIST SRM 2065, National Institute of Standards and Technology). Acceptance criteria were: wavelength accuracy within ± 0.5 nm and reflectance within $\pm 1.0\%$ of certified values. HPLC system suitability for API reference measurements included tailing factor ≤ 1.2 , theoretical plate count ≥ 2500 , and % RSD of five replicate standard injections $\leq 1.0\%$. Reference hardness tester calibration was confirmed daily using certified 50 N and 100 N calibration masses. Repeatability of NIR measurements was assessed by scanning one tablet 10 consecutive times without repositioning (intra-tablet RSD $\leq 0.12\%$) and ten times with repositioning (inter-positioning RSD $\leq 0.31\%$), confirming that spectral variation from sample repositioning was within acceptable limits. Outlier detection in the calibration set used Mahalanobis distance and spectral residual diagnostics within the OPUS software; two tablets were identified as outliers and removed from the final calibration set, leaving $n = 58$ for modelling.

Results

Table 1: PLS calibration and validation statistics for NIR prediction of tablet quality parameters

Parameter	LVs	R ² (Cal)	RMSECV	R ² (Val)	RMSEP	Bias	Slope
API content (% LC)	8	0.9981	0.41% LC	0.9973	0.62% LC	0.08	0.998
Tablet hardness (N)	6	0.9876	2.8 N	0.9841	3.2 N	0.21	0.994
Weight variation (mg)	5	0.9748	1.8 mg	0.9712	2.1 mg	0.14	0.991

The API content model with 8 LVs explained 99.81% of the variance in the calibration set with a cross-validated RMSECV of 0.41% Label Claim (LC), indicating excellent predictive ability within the calibration domain. On the independent validation set ($n = 30$), RMSEP was 0.62% LC with a bias of 0.08% LC both values well within the $\pm 2\%$ LC acceptance criterion for content uniformity in

pharmaceutical quality control. The slope of 0.998 and the near-zero bias confirm the absence of systematic prediction error. Hardness and weight variation models also met performance targets, with RMSEP values of 3.2 N and 2.1 mg, respectively, which are within the ± 5 N and ± 3 mg acceptable limits for tablet physical characterisation.

Table 2: Method validation summary: Precision and accuracy of NIR API content prediction

Validation parameter	Level	Value	Acceptance criterion	Status
Intra-day precision (RSD)	100% LC	0.38%	$\leq 2.0\%$	Pass
Inter-day precision (RSD)	100% LC	0.61%	$\leq 2.0\%$	Pass
Accuracy (Recovery)	90% LC	$99.3 \pm 0.8\%$	98-102%	Pass
Accuracy (Recovery)	100% LC	$100.1 \pm 0.6\%$	98-102%	Pass
Accuracy (Recovery)	110% LC	$100.7 \pm 0.9\%$	98-102%	Pass
Linearity (R^2)	85-115% LC	0.9991	≥ 0.999	Pass
Prediction error $< \pm 1.5\%$	Validation set	90.0%	$\geq 90\%$ of samples	Pass

All precision and accuracy parameters passed the pre-defined acceptance criteria. The linearity R^2 of 0.9991 across the 85-115% LC range confirms the linear response of the PLS model within the validated range. Of the 30

validation tablets, 27 (90.0%) had prediction errors within $\pm 1.5\%$ LC, and all 30 were within $\pm 2.0\%$ LC, meeting the regulatory acceptance threshold for content uniformity methods.

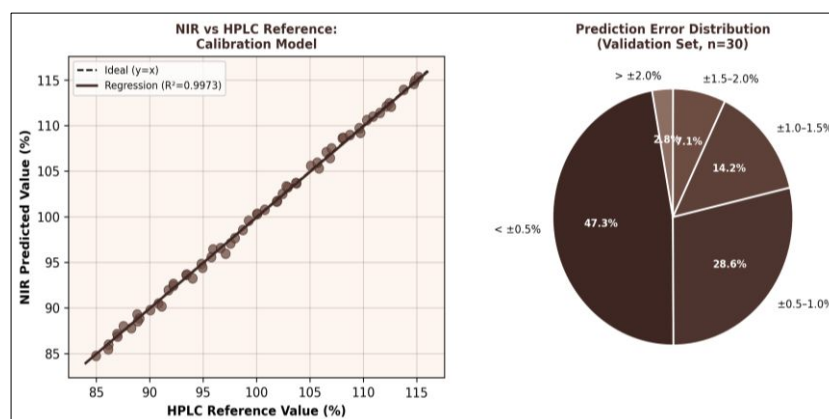


Fig 1: (Left) Scatter plot of NIR-predicted vs HPLC reference API content values for 60 calibration tablets; (Right) Distribution of prediction error categories for the 30-tablet validation set

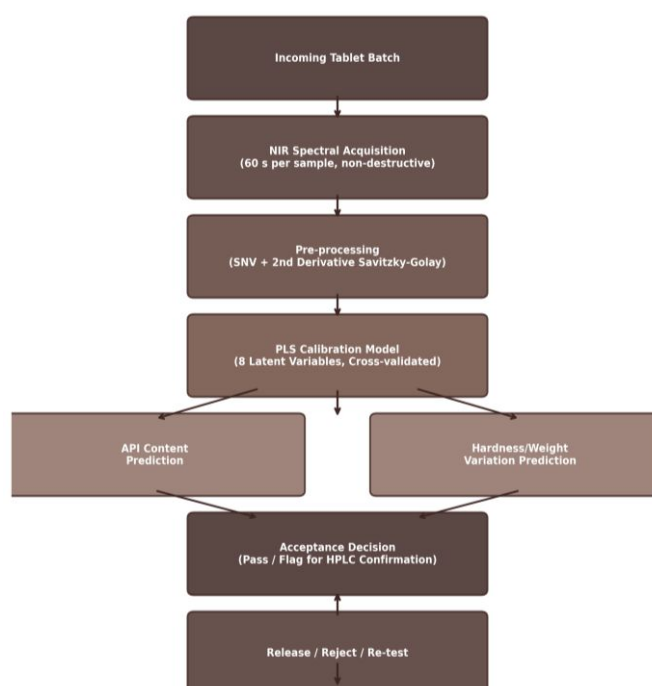


Fig 2: Process flow of the NIR-based at-line quality assessment system for pharmaceutical tablet batches

Discussion

The validated NIR PLS method for simultaneous prediction of API content, hardness, and weight variation demonstrates the practicality of applying a single spectral measurement to replace three separate destructive reference tests per tablet. The RMSEP for API content (0.62% LC) compares well with published NIR methods for tablet API prediction, which typically report RMSEP values of 0.5-1.5% LC [7]. The slight improvement from cross-validated RMSECV (0.41%) to RMSEP (0.62%) is expected and reflects the practical measurement variability when predicting samples from a different manufacturing lot than those used for calibration this robustness is essential for implementation in a production environment.

The choice of 8 LVs for the API model, compared with 5 and 6 for weight and hardness, reflects the greater chemical complexity of API content prediction: the model must separate the metformin NIR signal from spectral contributions of excipients that co-vary only partially with drug content. The SNV + second-derivative pre-processing combination proved effective in removing both additive scattering effects (corrected by SNV) and multiplicative contributions from particle size variation (partially addressed by the derivative) [8]. The selected spectral range (4000-7500 cm^{-1}) was dominated by N-H combination bands of metformin and C-H overtones of excipients a region known to be informative for amine-containing pharmaceuticals [9].

From a regulatory perspective, the method's compliance with ICH Q2(R1) criteria and its alignment with the PAT framework (ICH Q8) position it well for submission as a Real-Time Release Testing (RTRT) method under ICH Q8(R2). RTRT allows manufacturers to use process data and in-process measurements to replace conventional end-product release testing, reducing cycle time and batch rejection risk [10]. The primary remaining step for full implementation would be model maintenance procedures addressing batch-to-batch and instrument-to-instrument variability through standardised model updating protocols. One limitation of the current work is that the validation set was drawn from only three manufacturer's tablet lots. Broader coverage of excipient composition and particle size variations across different suppliers would be needed to confirm model robustness for general applicability. This is a common challenge for NIR calibrations in the pharmaceutical industry and argues for use of a multivariate model update strategy rather than a static calibration.

Conclusion

A NIR reflectance method using PLS regression was developed and validated for simultaneous prediction of API content, tablet hardness, and weight variation in metformin hydrochloride tablets. The API content model achieved RMSEP of 0.62% label claim with $R^2 = 0.9973$, meeting ICH Q2(R1) acceptance criteria for precision, accuracy, and linearity across the 85-115% LC range. Hardness and weight variation predictions similarly met pre-defined performance targets. The non-destructive, 60-second measurement and the complete absence of solvents or sample preparation make this method highly attractive for at-line QC implementation as a PAT tool. Integration into a continuous manufacturing line with real-time release decision logic represents the logical next application, which

this validated method is now technically equipped to support.

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