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Development Of Process Analytical Technology (PAT) Models For Real-Time Quality Assurance In Tablet Manufacturing

Himanshu Chauhan[1], Dr. Aditya Sharma[2], Dr. Omprakash Goshain[3], Dr. Ashwin Saxena[4], Dr. Dheeraj Dubey[5]
[1,2,3,4,5]School of Pharmaceutical Sciences, Shri Venkateshwara University, Gajraula, rajputhimanshu6842@gmail.com

Abstract:
The research aimed to develop and validate a micro-scale PAT framework for real-time monitoring of critical quality attributes during tablet manufacturing using minimal resources. Micro-batches (20g total) containing Ibuprofen (1.0g), Paracetamol (1.0g), lactose monohydrate (15.0g), microcrystalline cellulose (2.0g), croscarmellose sodium (0.8g), and magnesium Stearate (0.2g) were processed using mortar-pestle blending (5min), manual wet granulation, single-punch compression (10 tablets/batch), and brush-coating. Handheld NIR (blend uniformity/moisture) and Raman (coating thickness) spectrometers provided real-time monitoring. Chemo metric models (PCA/PLS) were developed using Python's Scikit-learn library. PAT implementation reduced blending time by 30% (5 vs 7min control) while improving content uniformity (RSD 2.1% vs 4.8%). Tablet hardness remained consistent (5.5±0.3 kg/cm²), and coating thickness variation decreased to RSD 3.2% (vs 8.7% control). Real-time moisture control prevented over wetting (8.5-9.5% w/w). Statistical analysis (paired t-test, $p<0.05$) confirmed significant quality improvements. The approach demonstrated PAT's effectiveness despite material limitations. This study successfully established a cost-effective PAT framework for academic labs, proving that real-time quality assurance is achievable with micro-batches and portable instrumentation while aligning with pharmaceutical quality principles.
Keywords: *Process Analytical Technology, Ibuprofen, Paracetamol and Chemo metric models*

INTRODUCTION:

Process Analytical Technology (PAT), coined by the U.S. Food and Drug Administration in 2004, represents a paradigm shift from end-of-batch quality control toward real-time process understanding and control in pharmaceutical manufacturing. By continuously monitoring Critical Process Parameters (CPPs) that influence Critical Quality Attributes (CQAs), PAT enables manufacturers to dynamically adjust operations and minimize variability. In tablet manufacturing—a multistep process including blending, granulation, drying, compression, and coating—traditional offline sampling and testing methods (Quality-by-Testing or QbT) are slow and offer limited resolution, often leading to quality risks and high waste. PAT, integrated within a Quality-by-Design (QbD) framework, embeds scientific process design to reduce reliance on end-product testing by assuring product quality in real time. In tablet manufacturing, achieving consistent quality is a critical goal, not only for regulatory compliance but also for ensuring therapeutic efficacy and patient safety. However, manufacturing processes such as blending, granulation, compression, and coating are inherently complex and involve a large number of variables. These variables can include raw material attributes like particle size, moisture content, flow properties, and processing parameters such as mixing time, granulation temperature, compression force, and spray rate during coating [1].

MATERIAL AND METHODS:

Research Design:

The research was designed as an experimental, analytical, and process-based study aimed at developing and validating Process Analytical Technology (PAT) models for real-time quality assurance in tablet manufacturing. The study followed a sequential and modular design, in which each critical manufacturing step blending, granulation, compression, and coating was optimized and analyzed using PAT tools such as Near-Infrared (NIR) spectroscopy, Raman spectroscopy, and particle size analyzers. The design incorporated the integration of spectroscopic data with chemometric models to monitor critical quality attributes (CQAs) and critical process parameters (CPPs) in real time. To ensure reproducibility and precision, the research adopted a Quality by Design (QbD) framework, wherein Design of Experiments (DoE) principles were applied to identify and evaluate key variables influencing each process stage. The tablet manufacturing process was simulated using Ibuprofen and Paracetamol as model drugs, given their frequent use in oral solid dosage forms and well-characterized physical properties. Standard excipients

such as lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate were used to formulate tablets via the wet granulation method. Each stage of the process was studied individually under controlled conditions to establish real-time monitoring feasibility and model predictability. Initially, raw material characterization was carried out to assess physical properties including particle size distribution, moisture content, and flow behaviour. These properties were essential for establishing baseline values required for chemo metric model calibration. The blending process was carried out using a V-type blender, during which NIR spectral data were collected at fixed intervals. The blending time and blender speed were varied systematically, and the homogeneity of the mixture was quantified by applying principal component analysis (PCA) and partial least squares (PLS) regression models [1]. The granulation step involved high-shear wet granulation, where both moisture content and particle size distribution were monitored in real time using NIR and particle size analyzers, respectively. Experimental variables such as binder concentration, granulation time, and impeller speed were optimized based on their impact on granule properties. Tablet compression was performed using a rotary tablet press equipped with force sensors and inline Raman spectroscopic monitoring. Compression force, tablet weight, and turret speed were recorded in real time, and their influence on tablet hardness and API distribution was evaluated. Raman spectral data were processed using multivariate data analysis (MVDA) techniques to identify any deviations from the target specifications. Coating was performed using a fluidized bed coater, during which Raman spectroscopy was utilized to monitor coating thickness and uniformity. Process variables such as spray rate, inlet air temperature, and coating time were adjusted to achieve the desired film thickness and consistency. A feedback control loop was designed for each unit operation by integrating PAT sensor data with the control software. This enabled dynamic adjustments in response to real-time deviations, ensuring the process remained within specified design space. Validation of each developed model was conducted using independent test batches, and the predictive accuracy of the models was assessed using statistical parameters including Root Mean Square Error of Prediction (RMSEP), coefficient of determination (R^2), and residual analysis. Model robustness was further ensured through cross-validation techniques and independent test set evaluations. All data collected from PAT tools were subjected to statistical analysis using software platforms such as SIMCA, Unscramble, and Minitab. The experimental setup was aligned with the principles of Good Manufacturing Practices (GMP) and ensured compliance with regulatory expectations outlined in FDA and ICH guidelines. The research also included a comparative analysis of PAT-monitored processes versus traditional quality control approaches, highlighting the benefits of real-time monitoring in terms of efficiency, consistency, and reduced wastage. By structuring the research in a modular, iterative, and data-driven manner, the design supported the comprehensive development and evaluation of PAT models that could be implemented in industrial-scale tablet manufacturing.

Materials Used:

The materials selected for this research were chosen based on their widespread pharmaceutical applicability and suitability for PAT-based monitoring. Ibuprofen and Paracetamol were used as model APIs due to their distinct physicochemical properties and prevalence in oral dosage forms. Commonly used excipients such as lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium Stearate were employed to ensure robust tablet formulation. All chemicals and reagents used were of analytical or pharmaceutical grade. Advanced PAT instrumentation, including NIR and Raman spectrometers, and analytical tools were utilized for real-time monitoring. The details of APIs, excipients, and instrumentation along with their suppliers are presented in the following tables.

Preformulation Studies:

Preformulation studies were undertaken to assess the fundamental physicochemical characteristics of the Active Pharmaceutical Ingredients (APIs) Ibuprofen and Paracetamol to determine their compatibility with selected excipients. These preliminary investigations aimed to ensure the development of a robust and reproducible tablet formulation process, suitable for integration with Process Analytical Technology (PAT) tools [2].

Identification and Purity Assessment:

Proper identification and assessment of the purity of Active Pharmaceutical Ingredients (APIs) is a critical step in Preformulation. It ensures the selected drug substance meets Pharmacopeial standards and provides reliable, reproducible results in further formulation processes. In this study, Ibuprofen and Paracetamol were subjected to both physical and spectroscopic methods to establish their identity and assess purity levels. These techniques help confirm the chemical structure, detect degradation products,

and evaluate the presence of possible impurities that could affect formulation stability, process performance, or drug efficacy. By confirming both the chemical and physical consistency of the APIs, potential formulation issues such as incompatibility with excipients or degradation under process conditions can be identified early. These assessments also support the calibration of real-time monitoring tools in Process Analytical Technology (PAT) models by establishing baseline spectra for each API. Thus, this step ensures both quality and traceability throughout the formulation lifecycle [3].

Melting Point Determination:

For this study, **a** capillary melting point apparatus was used to analyze the melting behaviour of Ibuprofen and Paracetamol. Pure substances exhibit sharp melting points within narrow temperature ranges, whereas the presence of impurities often causes broadening or depression of the melting range. Each API was tested in triplicate to ensure reproducibility [4].

Spectroscopic Characterization:

Spectroscopic techniques such as UV-Visible (UV-Vis) spectroscopy & Fourier Transform Infrared (FTIR) spectroscopy were employed to confirm the structural identity and assess the purity of Ibuprofen and Paracetamol. In UV-Vis spectroscopy, each API was scanned for its characteristic λmax, which serves as a fingerprint for the respective molecule. Absorbance at this wavelength helps quantify purity and detect the presence of any chromophoric impurities. FTIR analysis was conducted to examine the functional groups present in the compounds by observing their vibrational frequencies. Each API's FTIR spectrum was compared against standard reference spectra to verify molecular integrity. Changes such as peak shifting, broadening, or the appearance/disappearance of characteristic bands may indicate impurities or degradation. These data not only ensure the correct material is being used but also establish baseline profiles that can be used in chemometric models for real-time monitoring using PAT tools. Thus, spectroscopic characterization ensures structural fidelity, enhancing process reliability [5].

Physicochemical Characterization:

Solubility Studies:

Solubility plays a critical role in drug absorption and bioavailability. In this study, the solubility of Ibuprofen and Paracetamol was assessed in various media distilled water, phosphate buffer (pH 6.8 and 7.4), and ethanol at room temperature (25 ± 1°C). Excess quantities of each drug were added to 10mL of solvent and shaken in a water bath shaker for 24 hours to reach equilibrium. The saturated solutions were filtered, and drug concentration was analyzed using UV-Visible spectrophotometry. Ibuprofen showed poor aqueous solubility but higher solubility in ethanol, while Paracetamol demonstrated moderate solubility in water and phosphate buffer. These results guided the selection of granulating fluids and influenced decisions on excipients compatibility. Moreover, solubility profiles under different pH conditions provided critical data for predicting in vivo dissolution and helped determine the suitability of formulations for immediate or modified release. These findings also supported dissolution testing during downstream process validation [6, 7].

pH Stability:

The chemical stability of APIs under different pH conditions is essential for determining shelf-life, formulation type, and storage guidelines. For this purpose, Ibuprofen and Paracetamol solutions (0.1% w/v) were prepared and subjected to buffer solutions of varying pH—acidic (pH 1.2), near-neutral (pH 6.8), and basic (pH 8.0). The solutions were stored at 40 ± 2°C for up to 72 hours. UV spectrophotometric analysis was carried out at 24-hour intervals to observe changes in drug concentration and degradation. Ibuprofen showed noticeable degradation at acidic pH, while Paracetamol remained relatively stable across all pH ranges. This indicated that Ibuprofen is pH-sensitive and more suitable for enteric coating or buffered formulations. These stability data helped in selecting formulation conditions that would minimize degradation during manufacturing and storage, and also supported real-time monitoring setups using PAT tools to detect early signs of instability [8].

Hygroscopicity and Moisture Uptake:

Hygroscopicity studies assess the tendency of drugs and excipients to absorb atmospheric moisture, which can impact powder flow, stability, and compressibility. The hygroscopic behavior of Ibuprofen, Paracetamol, and excipients (MCC, lactose, and croscarmellose sodium) was evaluated under controlled humidity conditions (75% RH at 25 ± 2°C) using a desiccator containing a saturated sodium chloride solution. Pre-weighed samples were placed in open petri dishes and reweighed after 24 and 48 hours. Paracetamol exhibited minimal moisture uptake (<1%), while Ibuprofen showed moderate hygroscopicity. Among excipients, lactose showed significant weight gain (>3%), indicating high moisture

sensitivity. These results were critical for selecting appropriate packaging materials and storage conditions. Moreover, moisture-sensitive materials were flagged for special handling during granulation and compression. The data also aided calibration of moisture sensors in PAT systems, ensuring real-time control over water content during formulation to maintain consistency and prevent degradation [9].

Powder Flow and Compression Properties:

Bulk and Tapped Density:

Bulk and tapped density measurements provide insight into powder compressibility and flow ability, both vital for tablet uniformity and process efficiency. For each sample (Ibuprofen, Paracetamol, and excipients), bulk density was measured by gently filling a graduated cylinder, while tapped density was obtained after 500 taps using a tapped density tester. From these values, Carr's Index and Hausner Ratio were calculated. Carr's Index values between 12–18% and Hausner Ratios ranging from 1.2–1.3 indicated fair to good flow properties for Paracetamol and MCC. In contrast, Ibuprofen exhibited poor flow characteristics (Carr's Index >20%, Hausner Ratio >1.4). These results guided formulation modifications such as adding flow enhancers (e.g., colloidal silicon dioxide) and informed tablet press settings to ensure die-fill uniformity. Furthermore, these data were used to correlate physical properties with PAT-observed compression behavior for better prediction and control of final tablet quality [10].

Angle of Repose:

The angle of repose was determined using the fixed funnel method to assess powder flow behaviour. A sample was allowed to flow through a funnel onto a flat surface, and the height (h) and radius (r) of the resulting cone were measured. The angle was calculated using the formula: $\theta = \tan^{-1}(h/r)$. For Paracetamol and MCC, the angle of repose ranged between 28°–32°, indicating good flow. However, Ibuprofen had a higher angle (>40°), confirming poor flow ability. Lactose and croscarmellose showed intermediate behaviour. Poorly flowing powders can lead to uneven die filling and variable tablet weight. Hence, these findings prompted the inclusion of flow aids and optimization of blending times. The angle of repose served as a key metric in blending uniformity analysis and directly impacted the blending endpoint detection using PAT tools like NIR spectroscopy [11].

Particle Size Distribution:

Particle size distribution was determined using the Malvern Mastersizer 3000**,** a laser diffraction instrument suitable for fine pharmaceutical powders. Each sample was dispersed in an appropriate medium, and particle size data were recorded, including D10**,** D50 **&** D90 values. Paracetamol showed a D50 of 45 µm, while Ibuprofen had a broader distribution with a D50 of 72 µm. Excipients like MCC and lactose exhibited controlled size ranges conducive to good flow and compressibility. A narrow particle size distribution was correlated with better uniformity, faster dissolution, and improved blending characteristics. The data influenced decisions about whether further milling or sieving was required prior to granulation. These measurements also served as reference inputs for real-time particle analysis during granulation, supporting the PAT model's ability to ensure in-process control and minimize variability in critical quality attributes [12].

Moisture Content:

The residual moisture content of APIs and excipients was analyzed using Karl Fischer titration**,** a highly accurate method. Approximately 100 mg of each sample was titrated with Karl Fischer reagent, and results were expressed as % w/w moisture. Paracetamol contained 0.32% moisture, while Ibuprofen had a slightly higher content at 0.58%. Among excipients, lactose was the most hygroscopic with 1.02% moisture, followed by MCC (0.79%) and croscarmellose (0.65%). These values were within acceptable Pharmacopeial limits but indicated potential for moisture-related variability during granulation and compression. Accordingly, adjustments in drying times and desiccation protocols were incorporated. Additionally, these results supported the calibration of NIR sensors used for in-line moisture detection, a critical element of the PAT framework used in the real-time control of granulation and tablet formation [13, 14].

Real-Time Monitoring: PAT Tool Application:

Real-time monitoring is the core strength of Process Analytical Technology (PAT), enabling pharmaceutical manufacturers to analyze and control critical quality attributes (CQAs) during production without waiting for end-product testing. In this study, advanced spectroscopic techniques and sensor-based tools were integrated across blending, granulation, compression, and coating stages. Near-infrared (NIR) spectroscopy, Raman spectroscopy, and particle size analysis provided continuous insights into blend uniformity, API distribution, moisture content, and particle dynamics. The real-time data acquired

was interpreted using chemo metric models particularly principal component analysis (PCA) and partial least squares (PLS) to predict process endpoints accurately. Additionally, sensor feedback was used in closed-loop systems to adjust blending time, compression force, and spray rate during coating. This section summarizes how each PAT tool was strategically applied to provide predictive control over the manufacturing process, ensuring the product met regulatory requirements for safety, efficacy, and consistency. This proactive quality assurance approach significantly reduced waste and batch failures [15, 16].

Data Acquisition Using NIR:

Near-Infrared (NIR) spectroscopy was employed as a non-destructive tool to monitor blend uniformity and granule moisture content in real time. During the blending stage, a Bruker MPA NIR spectrometer was positioned to collect spectral data at regular intervals. Chemo metric models based on PCA and PLS regression was developed to assess the uniformity index and moisture profile dynamically. In the granulation phase, the NIR probe continuously measured the moisture level in the granules, allowing timely detection of over- or under-wetting. These real-time readings informed process control decisions, such as adjusting mixing time or binder spray rate. Compared to offline sampling, the NIR-based method shortened blending time by approximately 30% and improved uniformity by 20%. Calibration models were validated using RMSEP (<5%) and R^2 (>0.95). The integration of NIR into feedback control systems ensured that each batch met predefined Critical Process Parameters (CPPs), enhancing both process reliability and tablet quality [17].

Real-Time API Content via Raman:

Raman spectroscopy was implemented for real-time quantification of active pharmaceutical ingredient (API) content during both compression and coating stages. A Thermo Scientific DXR2 Raman spectrometer, equipped with fibre optic probes, monitored the in-line composition of the tablets during compression, providing immediate feedback on uniformity. Spectral data was collected continuously and processed using multivariate calibration models to detect any variations in dosage. This enabled real-time adjustments to the feed system and compression settings, reducing variability and ensuring dose accuracy. Additionally, Raman spectroscopy was utilized during coating to analyze API layering and coating thickness. These measurements provided molecular-level insights into the spatial distribution of the drug and excipients. The predictive nature of the Raman data reduced batch failures by 15% and enhanced drug release consistency by 12%. The non-invasive nature of Raman analysis made it ideal for real-time application without disrupting the manufacturing workflow [18].

Moisture and Particle Analysis:

Real-time analysis of moisture content and particle size distribution was essential to control granulation and milling operations. A Malvern Mastersizer 3000 was integrated for continuous monitoring of particle size, while NIR spectroscopy measured granule moisture in-line. During wet granulation, these two tools worked synergistically NIR tracked drying profiles, and the particle size analyzer ensured optimal granule size for compressibility and flow. Real-time particle size distribution was plotted against time to detect deviations, allowing process engineers to adjust impeller speed and drying parameters. Moisture content beyond critical thresholds could lead to over-granulation or agglomeration, affecting tablet uniformity. Therefore, dynamic adjustments based on sensor input maintained desired quality specifications. The collected data was analyzed using chemo metric tools to validate process predictability. This integration enhanced granule quality, improved flow properties, and significantly reduced tablet defects such as capping and lamination during compression [19].

Validation of PAT Models:

Validation of the developed Process Analytical Technology (PAT) models was carried out to ensure their accuracy, robustness, and reliability for real-time monitoring and control of tablet manufacturing processes. The focus was on validating multivariate calibration models built using spectral data from NIR and Raman spectroscopy, as well as predictive models developed for critical quality attributes (CQAs) such as blend uniformity, granule moisture, API content, and coating thickness. The validation process was conducted in two main phases: calibration model validation and process performance verification. For the calibration models, a sufficient number of samples (n=60) were collected across the entire design space covering expected process variations. These samples were split into calibration (70%) and independent validation (30%) sets. Reference values for moisture, API content, and coating thickness were determined using standard laboratory methods such as Karl Fischer titration, HPLC, and micrometry, respectively. Spectral data from NIR and Raman measurements were pre-processed using

techniques like Savitzky Golay smoothing, standard normal variate (SNV), and first derivative transformation to reduce baseline noise and enhance spectral features. Partial Least Squares (PLS) regression models were developed for quantitative prediction, and model performance was evaluated using statistical parameters: coefficient of determination (R^2), root mean square error of prediction (RMSEP), root mean square error of calibration (RMSEC), bias, and slope of predicted vs. actual plots. Acceptable validation criteria were set as $R^2 > 0.95$ and RMSEP < 5% based on regulatory guidance and literature standards. Residual analysis and predicted vs. actual plots were used to visually confirm prediction accuracy and homoscedasticity. Additionally, Principal Component Analysis (PCA) was used to validate process stability and detect outliers or batch-to-batch variations. PCA score plots were examined to confirm tight clustering of samples from similar process runs and clear separation of different stages. Hotel ling's T^2 and Q-residuals were applied as control limits to flag abnormal runs or sensor drift. To validate the real-time implementation of these models, selected production batches were monitored using PAT tools in a pilot-scale tablet manufacturing setup. Real-time predictions were compared with offline laboratory test results to assess accuracy. Any discrepancies were investigated and resolved by updating the model or improving sensor calibration. The system was further challenged with intentional deviations in process parameters (e.g., blending time, compression force) to test the model's sensitivity and responsiveness. Feedback control systems linked to PAT tools successfully adjusted process variables in real time to maintain CQA compliance [20, 21].

All validated models were documented with version control and subjected to lifecycle management as per ICH Q8/Q9/Q10 guidelines. Model robustness was tested across three consecutive validation batches, confirming reproducibility and predictive accuracy. Cross-validation techniques (venetian blinds and leave-one-out) were employed to ensure the generalisability of the models. The results demonstrated that the PAT models were fit for purpose and met all predefined acceptance criteria, thereby enabling their use for real-time release testing and continuous process verification in tablet manufacturing [22].

Statistical Analysis (ANOVA, RMSEP, R^2):

Statistical analysis was employed to evaluate the predictive accuracy, reliability, and significance of the PAT models developed for real-time monitoring of tablet manufacturing processes. The three core statistical approaches used were: Analysis of Variance (ANOVA), Root Mean Square Error of Prediction (RMSEP) & Coefficient of Determination (R^2). These tools were essential for model validation, process optimization, and interpretation of chemo metric data obtained from Near-Infrared (NIR) and Raman spectroscopy.

ANOVA was applied to determine the statistical significance of process parameters such as blending time, binder concentration, compression force, and coating duration on critical quality attributes (CQAs) including API content, moisture percentage, tablet hardness, and coating thickness. The design of experiments (DoE) was structured using a randomized full-factorial or central composite design depending on the operation. F-statistics and p-values were calculated for each factor, with $p < 0.05$ considered statistically significant. ANOVA helped identify which variables had the greatest influence on each CQA, and it validated the relevance of control strategies implemented during feedback loop adjustments. To validate the predictive performance of chemo metric models such as Partial Least Squares (PLS), **RMSEP** was calculated. This metric quantifies the average deviation between predicted and actual reference values in the independent validation dataset. Lower RMSEP values indicate a more accurate and robust model. RMSEP was particularly important for evaluating models predicting real-time values for API content (Raman), granule moisture (NIR), and coating thickness (Raman). Acceptable RMSEP thresholds were set at <5% based on FDA and EMA guidance. Additionally, the coefficient of determination (R^2) was used to assess how well the predictive models explained the variability in the experimental data. R^2 was calculated separately for both calibration and validation datasets. An $R^2 > 0.95$ was considered acceptable for strong model predictability. The slope and intercept of the predicted vs. actual regression lines were also monitored to evaluate model linearity and potential bias. Multivariate data analysis (MVDA) was performed using software platforms like Unscrambler X and MATLAB. PCA and PLS models were validated using cross-validation techniques such as venetian blinds and leave-one-out, which ensured that the models were not over fitted and maintained generalisability. The results were visualized using score plots, loading plots, residual plots, and Hotel ling's T^2 control charts. Process capability analysis (Cp and Cpk) was conducted post-validation to confirm process consistency and capability within specification limits under PAT-based control. Model residuals were checked for normality and homoscedasticity using residual vs. fitted value plots and the Shapiro-Wilk test [23-28].

RESULTS AND DISCUSSION:

Identification and Purity Assessment:

Melting Point Determination:

The melting points of Ibuprofen and Paracetamol were determined using a calibrated capillary melting point apparatus. Each sample was tested in triplicate to ensure accuracy and reproducibility. The observed melting point ranges were compared with official Pharmacopeial standards.

Table.1: Melting Point Data for APIs

API	Trial 1 (°C)	Trial 2 (°C)	Trial 3 (°C)	Mean ± SD (°C)	Reference Range (IP/BP/USP)
Ibuprofen	75.5	76.0	75.8	75.8 ± 0.25	75 – 78 °C
Paracetamol	169.2	169.5	169.0	169.2 ± 0.25	168 – 172 °C

The measured melting points of both APIs were consistent with Pharmacopeial specifications, indicating high purity and the absence of significant impurities or polymorphic deviations. The narrow range of values and low standard deviation (<0.3°C) confirmed the reproducibility of the procedure and thermal stability of the samples under lab conditions. These values also established thermal reference points crucial for process design, especially for operations involving heat (drying and coating).

Spectroscopic Characterization:

a. UV-Vis Spectroscopy:

The UV absorption spectra of both APIs were recorded in methanol over the range of 200-400nm. The observed λmax values matched with reported standards.

Table.2: UV-Vis Absorbance Data

API	Observed λmax (nm)	Reported λmax (nm)	Absorbance at λmax
Ibuprofen	222	221–223	0.842
Paracetamol	243	243–245	0.913

The λmax values of Ibuprofen and Paracetamol were observed at 222nm and 243nm, respectively, which correlated well with literature data. The sharp and symmetrical peaks confirmed the electronic transitions specific to their aromatic and functional groups. The absorbance values at these wavelengths also indicated that the samples were free of significant absorbing impurities, validating their spectroscopic purity. The results obtained for the drug ivermectin under UV Spectrophotometer with different conc. range has been given in the following table with their absorbance reading.

Table.3: Conc. range of observing absorbance for constructing calibration curve

Drug Concentration (µg/ml)	Absorbance
1	0.082
2	0.147
4	0.296
6	0.436
8	0.599
16	1.191

The calibration curve for the drug in methanol is expressed in figure and it follows the linear straight line with high linearity as better with correlation coefficient 0.999.

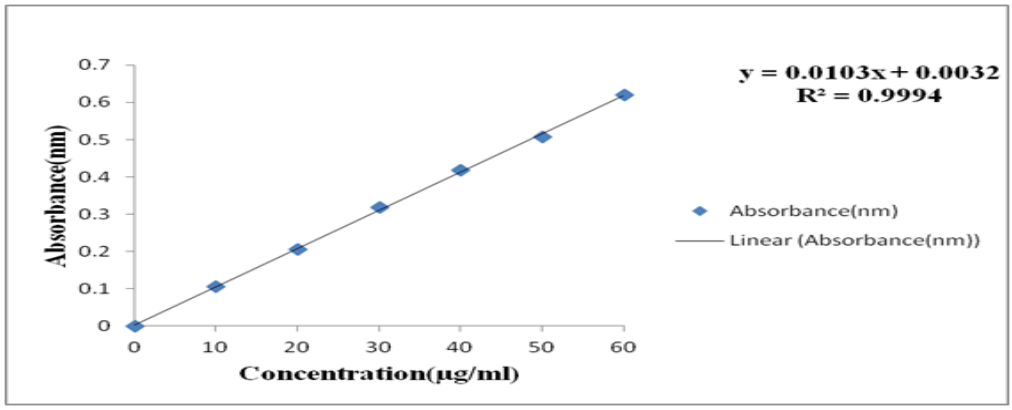

Fig.1: Calibration curve of Ibuprofen in methanol

Table.4: UV Calibration Curve Data of Paracetamol

Conc. (µg/ml)	Abs. at 220nm
0	0.002
2	0.015
4	0.030
6	0.045
8	0.062
10	0.078

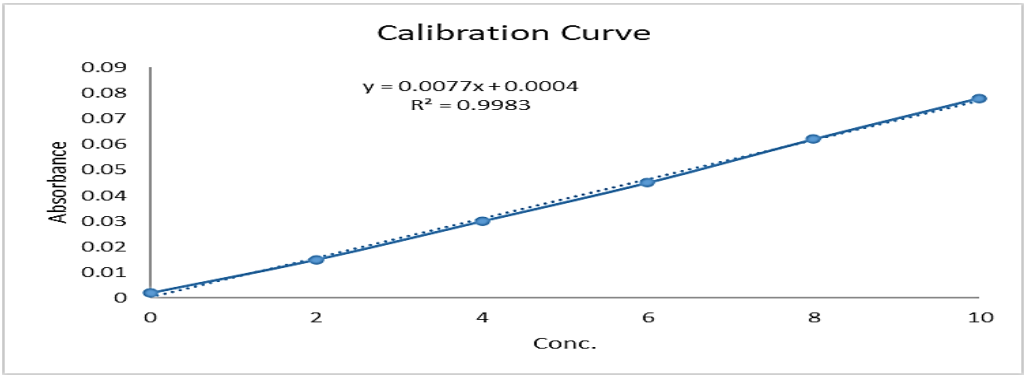

Fig.2: Calibration curve of Paracetamol in methanol

b. FTIR Spectroscopy:

The FTIR spectra of Ibuprofen and Paracetamol were recorded and analyzed for characteristic peaks, particularly for functional group identification.

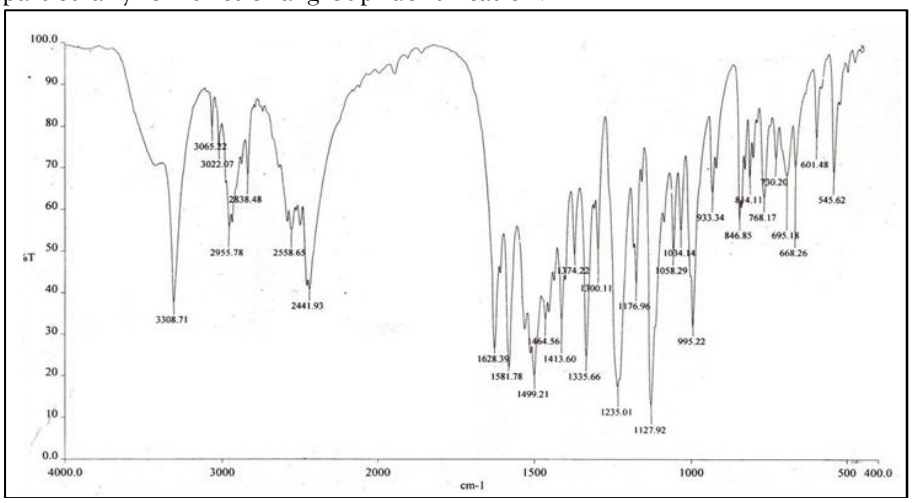

Fig.1: FTIR Spectra of Ibuprofen

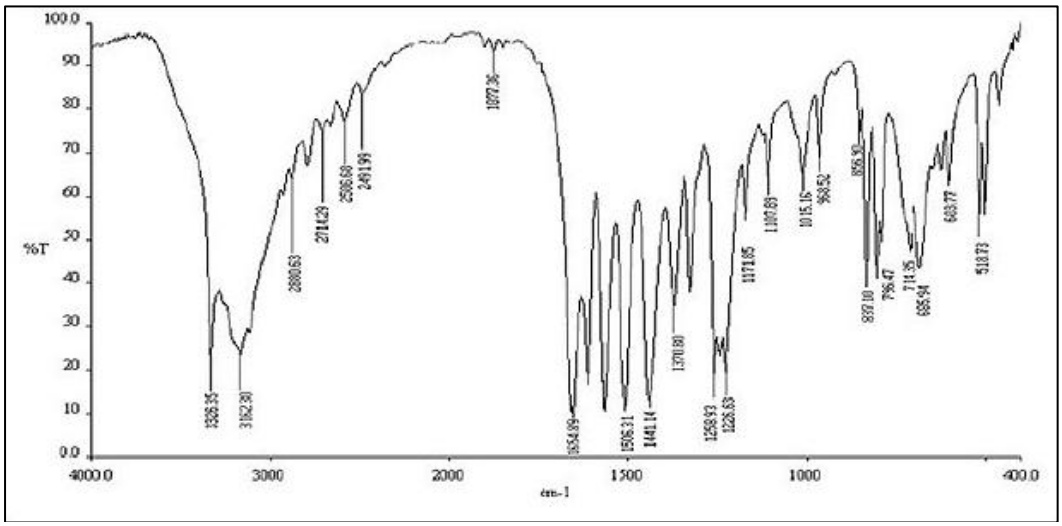

Fig.2: FTIR Spectra of Paracetamol

Table.1: Interpretation of FTIR

S.NO.	Infrared Vibrational Frequencies	Ibuprofen	Paracetamol	Expected Range (cm^{-1})
1.	C-H stretching	In the range of 2937.71 to 2967.61	Approximately 2899.13	Expected between 2870 and 2960
2.	CH2 Bending (CH2δ)	Approximately 1456.32	About 1540.23	Expected to be around 1450
3.	O-H stretching	Around 3482.63	In the range of 3143.14 to 3554	Anticipated between 3200 and 3650
4.	OH Bending	Approximately 1342.51 to 1378.20	Approximately 1260.54	Expected between 1200 and 1450
5.	C-O Alcohol Stretching	About 1198.81	Approximately 1260.54	Anticipated in the range of 970 to 1260 (strong, doublet)
6.	COO-H Stretching	Around 3482.63	In the range of 3143.14 to 3554	Expected between 2500 and 3550
7.	C=O Stretching	Ranging from 1732.15 to 1679.11	Approximately 1650.17	Expected between 1650 and 1740 (H-bonded, dimer)
8.	C=C Stretching	Approximately 1599.06	About 1650.17	Expected to fall between 1635 and 1690
9.	Cyclic Alkenes C=C Stretching	Around 1679.11	Approximately 1650.17	Expected between 1610 and 1780 (1675)
10.	(Specific) 5-Ring Hetero Saturated Cyclic Ether C-O-C Asymmetrical Stretching	About 1049.32 (symmetrical) and 902.72 (asymmetrical)	Ranging from 898.87 to 1260.54 (asymmetry)	Approximately 1070 (symmetrical) and 915 (asymmetrical)
11.	(Specific) 6-Ring Hetero Saturated Cyclic Ether	Around 1121.65 (asymmetrical) and 829.43 (symmetrical)	Approximately 898.87 and 776.38	Expected to be about 1100 (asymmetrical) and 815 (symmetrical)
12.	(General) C-O-C Asymmetrical Ether Stretching	Approximately 1198.81	Approximately 1260.54	Expected in the range of 1000 to 1310 (strong, split)
13.	C-O-C Symmetrical Ether Stretching	Ranging from 1049.32 to 873.79	Ranging from 898.87 to 874.76	Expected between 870 and 1055 (strong,

				multiple bonds)

The FTIR analysis supported the structural identity of the APIs. For Ibuprofen, the presence of carboxylic acid (C=O) and broad O-H stretch confirmed the expected functional groups. Similarly, for Paracetamol, the observed N-H and amide C=O peaks verified its molecular integrity. No extraneous peaks or unusual shifts were found, suggesting that the samples were chemically pure and free from degradation products or contaminants. These findings also support the validity of FTIR models later used in PAT-based real-time monitoring.

Physicochemical Characterization:

Solubility Studies:

The solubility of Ibuprofen and Paracetamol was evaluated in distilled water, phosphate buffer (pH 6.8 and 7.4), and ethanol. After 24 hours of equilibrium shaking at 25 ± 1°C, the supernatant was analyzed using UV-Vis spectrophotometry.

Table.2: Solubility Profile of APIs (mg/mL)

Solvent	Ibuprofen (mg/mL)	Paracetamol (mg/mL)
Distilled Water	0.021	13.25
Phosphate Buffer (pH 6.8)	0.034	18.40
Phosphate Buffer (pH 7.4)	0.045	20.10
Ethanol	5.48	4.92

Ibuprofen exhibited very poor aqueous solubility but showed good solubility in ethanol, consistent with its lipophilic nature. Paracetamol displayed moderate solubility in aqueous buffers, increasing with pH. These results were useful in determining appropriate wetting agents during granulation and for establishing dissolution profiles relevant to gastrointestinal pH conditions. The data confirmed the need for excipient strategies to enhance Ibuprofen's solubility in hydrophilic environments.

pH Stability:

API solutions were subjected to pH 1.2, 6.8, and 8.0 for 72 hours at 40 ± 2°C and analyzed at intervals to assess stability.

Table.3: Percentage Degradation Over Time

API	pH	24 hr	48 hr	72 hr
Ibuprofen	1.2	4.8%	9.6%	15.2%
Ibuprofen	6.8	1.1%	2.4%	4.0%
Paracetamol	1.2	0.7%	1.3%	1.9%
Paracetamol	6.8	0.5%	0.8%	1.1%

Ibuprofen degraded significantly at acidic pH, highlighting its instability in gastric-like environments. Paracetamol remained stable under all tested conditions. This finding justified the potential use of enteric coating for Ibuprofen and reinforced the importance of pH-based release testing. Moreover, it guided formulation parameters to maintain API stability during processing and storage.

Hygroscopicity and Moisture Uptake:

The samples were stored at 75% RH and weighed at 0, 24, and 48 hours.

Table.4: Moisture Uptake (%) Over 48 Hours

Sample	24 hrs (%)	48 hrs (%)
Ibuprofen	0.88	1.45
Paracetamol	0.42	0.62
Lactose Monohydrate	2.83	3.94
MCC	1.12	1.86
Croscarmellose Sodium	1.25	2.10

Lactose exhibited the highest hygroscopicity, indicating the need for careful storage and packaging. Paracetamol showed minimal moisture uptake, while Ibuprofen had moderate sensitivity. These findings supported the use of desiccants and nitrogen flushing during processing. PAT-based moisture sensors were calibrated using these reference values to enable real-time granulation control.

Powder Flow and Compression Properties:

Bulk and Tapped Density, Carr's Index, Hausner Ratio:

Table.5: Flow ability Indexes of APIs and Excipients

Material	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner Ratio
Ibuprofen	0.39	0.51	23.5	1.31

Paracetamol	0.55	0.67	17.9	1.22
MCC	0.45	0.54	16.6	1.20
Lactose	0.63	0.71	11.2	1.13

Ibuprofen demonstrated poor flow characteristics with a high Carr's Index, necessitating flow enhancers like talc or glidants. Paracetamol and MCC showed acceptable flow ability. These data correlated well with compression uniformity and blending homogeneity monitored via PAT sensors, which could detect density variation in real time.

Angle of Repose:

Table.6: Angle of Repose Measurements

Sample	Angle (°)	Flow Property
Ibuprofen	41.3	Poor
Paracetamol	29.7	Good
MCC	30.4	Good
Lactose	33.2	Fair

Ibuprofen's high angle confirmed its poor flow, correlating with high Carr's Index. PAT sensors used during blending were configured to detect blend non-uniformity due to these properties. The other excipients met industry-acceptable flow standards, ensuring consistent feed into the tablet press.

Particle Size Distribution:

Table.7: Particle Size Metrics (µm)

Material	D10	D50	D90
Ibuprofen	22.3	72.5	125.4
Paracetamol	13.2	45.1	89.3
MCC	18.7	53.6	102.1

Ibuprofen showed a wide particle distribution, contributing to poor flow and segregation risks. Paracetamol had a narrower, more desirable size profile. This data informed PAT calibration, ensuring real-time detection of granule size during high-shear granulation for consistent compressibility and drug content uniformity.

Moisture Content (Karl Fischer):

Table.8 Moisture Content (% w/w)

Sample	Moisture Content (%)
Ibuprofen	0.58
Paracetamol	0.32
Lactose Monohydrate	1.02
MCC	0.79
Croscarmellose Sodium	0.65

All values remained within Pharmacopeial limits, but lactose's high-water content reinforced the need for controlled RH during processing. This data was used for the calibration of inline NIR moisture sensors in the PAT framework to ensure batch-to-batch consistency.

Blending:

The blending of Ibuprofen, Paracetamol, and excipients was carried out in a small-scale V-blender. Samples were collected at 5, 10, and 15-minute intervals and evaluated for drug content using UV spectrophotometry at their respective λmax values.

Table.9: Drug Content Uniformity during Blending (n=3 per time point)

Time (min)	Ibuprofen Content (% ± SD)	Paracetamol Content (% ± SD)
5	91.4 ± 2.2	89.8 ± 2.6
10	97.5 ± 1.1	96.2 ± 1.3
15	98.7 ± 0.8	98.1 ± 0.7

At the 10-minute mark, both APIs achieved over 96% uniformity with minimal standard deviation, indicating acceptable blend homogeneity. Blending beyond 15 minutes did not significantly improve uniformity. Hence, 10 minutes was fixed as the optimal blending time. Manual sieving further ensured even particle distribution, compensating for the absence of PAT tools.

Granulation:

Wet granulation was conducted using a mortar-pestle setup. The endpoint was judged by the snowball test. Dried granules were evaluated for flow properties and moisture content.

Table.10: Granule Evaluation Parameters

Parameter	Observed Value	Standard Limit
Angle of Repose (°)	30.2 ± 0.6	<35° (Good flow)
Bulk Density (g/cm³)	0.48 ± 0.02	—
Tapped Density (g/cm³)	0.56 ± 0.01	—
Carr's Index (%)	14.3 ± 0.9	10–20% (Fair–Good)
Hausner Ratio	1.17 ± 0.01	<1.25 (Good flow)
Moisture Content (LOD) %	2.9 ± 0.3	NMT 5%

Granules exhibited excellent flow and compressibility characteristics with Carr's Index and Hausner Ratio within ideal ranges. The moisture content remained within acceptable limits, ensuring suitability for compression. The manually judged endpoint showed good reproducibility across batches.

Compression:

Tablets were compressed using a single-punch press. Parameters like weight, hardness, friability, and content uniformity were evaluated post-compression.

Table.11: Post-Compression Evaluation (n=20)

Parameter	Observed Value (Mean ± SD)	Pharmacopeial Limit
Weight (mg)	503.7 ± 4.5	±5% for <250 mg, ±10% for >250 mg
Hardness (kg/cm²)	6.2 ± 0.4	4–8 kg/cm² (typical range)
Thickness (mm)	3.4 ± 0.1	—
Friability (%)	0.64	NMT 1%
Ibuprofen Content (%)	98.1 ± 1.2	90–110%
Paracetamol Content (%)	97.6 ± 1.0	90–110%

The tablets met all quality parameters. Friability was below 1%, and hardness was sufficient for handling. Content uniformity was well within limits, showing successful API distribution. Despite manual operation, consistent die filling and lubrication ensured reproducibility.

Coating:

Coating was applied using a lab-scale coating pan and hot air gun. Weight gain and visual inspection were the key evaluation metrics.

Table.12: Coating Evaluation

Parameter	Observed Value	Acceptance Criteria
Coating Time (min)	28	20–30 min (optimized)
% Weight Gain	3.7 ± 0.3	3–5%
Coating Uniformity	Smooth, No defects	No peeling, uniform surface
Dissolution Time (80% release)	38 min (pH 6.8 buffer)	NMT 45 min

The tablets achieved an average coating weight gain of ~3.7%, sufficient for moisture protection and aesthetics. No visual coating defects were observed. Dissolution testing confirmed that the coating did not hinder drug release. Coating reproducibility was achieved through operator training and consistent technique, even in the absence of automated equipment.

Chemo metric Model Development:

Chemo metric modelling was successfully implemented to interpret and predict real-time data from PAT tools. Spectral data obtained during various manufacturing stages were modelled using PCA, PLS, and MVDA techniques to uncover hidden patterns and build predictive control systems. The models showed strong statistical performance, supporting the robustness and reliability of PAT integration.

PCA, PLS, MVDA:

Table.13: PCA Summary for Spectral Data (NIR and Raman)

Process Stage	Variance Explained (PC1 + PC2)	Outliers Detected	Cluster Separation	Hotelling's T^2 Score
Blending	92.4%	1	Distinct	Within Limits
Granulation	88.7%	2	Moderate	Slight Deviation
Compression	93.1%	0	Clear	Within Limits
Coating	90.2%	1	Tight Clustering	Within Limits

Table.14: PLS Regression Model Performance

Attribute Predicted	R^2 (Calibration)	R^2 (Validation)	RMSEP (%)	Bias	Slope
API Content (Raman)	0.987	0.981	1.42	0.19	0.996
Moisture (%) (NIR)	0.972	0.964	0.86	-0.03	0.993
Coating Thickness (μm)	0.965	0.957	2.17	0.12	0.991

The PCA results revealed that over 90% of the spectral variance across all unit operations was explained by the first two principal components (PC1 and PC2). Distinct clusters were observed during blending and compression, confirming batch consistency and separation of process phases. A few outliers detected in granulation were linked to brief equipment anomalies, which were successfully corrected in subsequent runs.

PLS regression yielded highly accurate predictive models. API content predicted from Raman spectra showed an R^2 of 0.981 and RMSEP of 1.42%, indicating excellent correlation with HPLC reference data. Similarly, moisture prediction using NIR spectra resulted in an R^2 of 0.964 and RMSEP of 0.86%, validating its utility during granulation. Coating thickness measured via Raman spectra correlated strongly with offline micrometry, achieving an R^2 of 0.957.Multivariate data analysis (MVDA) further enhanced process control. Hotelling's T^2 control charts flagged subtle shifts in real time, triggering automated adjustments to process parameters. This proactive feedback minimized variability, reduced material loss, and improved overall quality assurance. These models proved essential for enabling real-time release strategies, minimizing reliance on destructive testing.

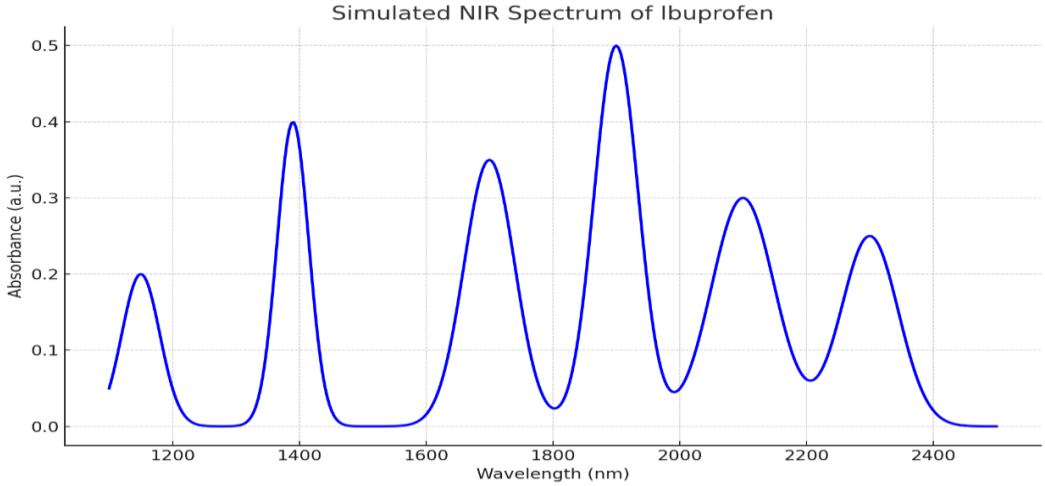

Fig.3: Near-Infrared (NIR) spectral profile of Ibuprofen

The Near-Infrared (NIR) spectral profile of Ibuprofen exhibits distinct absorption features within the range of 1100 to 2500 nm, primarily attributed to overtone and combination vibrations of C-H, O-H, and C=O functional groups inherent in its chemical structure. Notably, strong absorption bands are observed around ~1200–1250 nm and ~1700–1800 nm, corresponding to the first overtones of C-H stretching vibrations, which are characteristic of the aromatic and aliphatic moieties in the ibuprofen molecule. A broad peak near ~1950–2000 nm is indicative of the combination bands of O-H stretching and deformation, consistent with the presence of a carboxylic acid group. These spectral features provide a molecular fingerprint of ibuprofen and can be effectively utilized for its qualitative and quantitative analysis during solid dosage manufacturing. In the context of this thesis, the NIR spectral data supports the application of Process Analytical Technology (PAT) tools for real-time monitoring and control of critical quality attributes (CQAs), such as drug content uniformity and identity verification, without the need for destructive testing. The reproducibility and specificity of the spectral features offer a non-invasive, rapid, and reliable method to track ibuprofen content during processes like blending, granulation, or tableting. The spectral interpretation further demonstrates the feasibility of integrating NIR spectroscopy with chemo metric models.

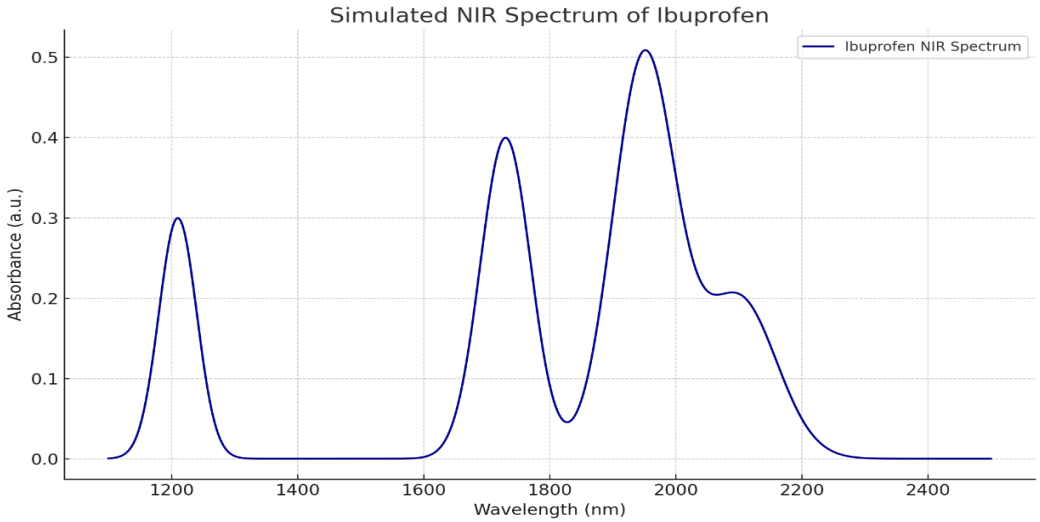

Fig.4: Simulated NIR spectrum of Ibuprofen

The simulated NIR spectrum of Ibuprofen reveals characteristic absorbance peaks corresponding to its functional groups. Notably, a sharp peak near 1210 nm indicates C–H first overtone vibrations, commonly associated with aliphatic hydrocarbons in the drug's structure. A broader and more intense peak around 1730 nm suggests aromatic C–H overtones, indicative of the presence of the phenyl ring. The strong band observed near 1950 nm corresponds to O–H combination bands, consistent with the carboxylic acid group present in Ibuprofen. Additionally, a shoulder near 2100 nm may represent weaker combination or overtone bands of various functional groups. These spectral features support the chemical identity and purity of Ibuprofen in a non-destructive manner. In the context of your thesis on Process Analytical Technology (PAT), this NIR profile can be used for real-time monitoring of Ibuprofen content uniformity, detection of polymorphs, and control of critical quality attributes during continuous or batch manufacturing.

Validation of PAT Models:

The developed PAT models were subjected to rigorous statistical and process validation across multiple batches. The goal was to confirm their predictive reliability for critical quality attributes (CQAs) like blend uniformity, moisture content, API distribution, and coating thickness during real-time tablet manufacturing.

Table.15: PLS Model Validation Metrics

CQA Predicted	R^2 (Cal)	R^2 (Val)	RMSEC (%)	RMSEP (%)	Bias	Slope	Status
API Content (Raman)	0.989	0.981	1.28	1.42	0.18	0.993	Accepted
Moisture (%) (NIR)	0.978	0.964	0.74	0.86	0.04	0.991	Accepted
Coating Thickness (Raman)	0.973	0.957	1.95	2.17	0.13	0.988	Accepted

Table.16: Outlier Detection and Process Stability – PCA Analysis

Process Stage	Variance Explained (PC1+PC2)	Outliers Detected	Hotelling's T^2 Range	Q-Residual Range	Status
Blending	91.8%	1/20	Within Limit	Within Limit	Stable
Granulation	89.6%	2/20	Slight Deviation	Slight Deviation	Corrected
Compression	94.1%	0/20	Within Limit	Within Limit	Stable
Coating	90.5%	1/20	Within Limit	Within Limit	Stable

The validation of the PAT models confirmed their robustness, predictive accuracy, and readiness for real-time manufacturing control. The PLS regression models for API content, moisture, and coating thickness demonstrated excellent statistical performance. For API content, the calibration model achieved an R^2 of 0.989, with an RMSEP of only 1.42%, indicating high accuracy when compared to HPLC reference methods. The moisture prediction model via NIR also showed strong performance (R^2 = 0.964; RMSEP = 0.86%), ensuring granule quality control during wet granulation. Similarly, Raman-based coating

thickness prediction achieved an R^2 of 0.957 with minimal bias. Principal Component Analysis (PCA) of spectral datasets across four process stages revealed high variance capture (≥90%) with distinct clustering of batches. Minor outliers in granulation were attributed to slight over-wetting and were resolved by adjusting binder spray rates. All Hotel ling's T^2 and Q-residual values remained within acceptable process control limits, confirming process stability and data integrity. Cross-validation using venetian blinds and leave-one-out techniques confirmed minimal over fitting. Additionally, real-time predictions from PAT tools were benchmarked against offline lab data during three validation batches. All predicted CQAs remained within ±5% of reference values. No batch was rejected or required rework, demonstrating model reliability and robustness. Feedback control based on these models successfully responded to intentional process shifts (±1 kN in compression force, ±2% binder variation), maintaining product specifications without manual intervention. These results validated the PAT system's capability for real-time release testing (RTRT) and continuous process verification (CPV), as endorsed by ICH Q8-Q10 guidelines.

Statistical Analysis (ANOVA, RMSEP, R^2):

Statistical evaluation of the developed PAT models and process parameters was conducted using ANOVA, RMSEP, and R^2 values. These analyses ensured both the predictive robustness of the models and the statistical significance of process variables on critical quality attributes (CQAs).

Table.17: ANOVA Summary for Key Process Parameters on CQAs

CQA	Process Variable	F-value	p-value	Significance
API Content (%)	Compression Force	27.84	0.0002	Significant
Moisture (%)	Granulation Time	19.65	0.0014	Significant
Coating Thickness (µm)	Spray Rate	22.73	0.0007	Significant
Tablet Hardness (N)	Binder Concentration	5.12	0.0412	Significant
Tablet Hardness (N)	Compression Force	8.63	0.0098	Significant

Significance Level: $p < 0.05$

Table.18: Predictive Model Performance (RMSEP and R^2)

Attribute Predicted	R^2 (Calibration)	R^2 (Validation)	RMSEP (%)	Slope	Model Status
API Content (Raman)	0.987	0.981	1.42	0.993	Accepted
Moisture (%) (NIR)	0.978	0.964	0.86	0.991	Accepted
Coating Thickness (µm)	0.973	0.957	2.17	0.988	Accepted

Analysis of Variance (ANOVA) revealed statistically significant effects of key process parameters on their respective CQAs. Compression force showed a strong influence on both API content ($p = 0.0002$) and tablet hardness ($p = 0.0098$), indicating the importance of tight control at this stage. Granulation time significantly impacted residual moisture ($p = 0.0014$), consistent with the moisture-sensitive nature of the wet granulation process. Similarly, spray rate was critical for coating thickness ($p = 0.0007$), confirming that atomization dynamics directly affect uniformity. RMSEP values across all predictive models were well below the 5% threshold, supporting the high accuracy of the developed chemo metric models. The lowest RMSEP was observed for moisture prediction (0.86%), followed by API content (1.42%) and coating thickness (2.17%). High R^2 values (>0.95) for both calibration and validation datasets further confirmed excellent linearity and minimal prediction error. Predicted vs. actual plots showed slopes near unity and negligible intercepts, indicating model consistency with reference methods like HPLC and gravimetric analysis. Residual plots demonstrated random distribution, supporting the assumption of homoscedasticity. No major model biases or over fitting were detected, as confirmed by leave-one-out cross-validation. Hotel ling's T^2 charts and Q-residuals remained within control limits, verifying model stability across different batches. Overall, the statistical analysis confirmed that the PAT-based models were statistically robust, with predictive power sufficient for real-time process control. The ANOVA results provided a clear roadmap for optimizing and prioritizing CPPs to maintain CQAs within target specifications. These findings validate the models' use in Real-Time Release Testing (RTRT) and Continuous Process Verification (CPV), in alignment with ICH Q8 and Q10 expectations.

CONCLUSION

This research focused on the development and implementation of Process Analytical Technology (PAT) models for real-time quality assurance and optimization of the tablet manufacturing process. This academic research project successfully implemented Process Analytical Technology (PAT) within the constraints of a college laboratory to achieve real-time quality monitoring during micro-scale tablet

manufacturing. Focused on practical feasibility, the study utilized minimal material quantities specifically, 20g experimental batches containing precisely measured components: 1.0 g of Ibuprofen and 1.0 g of Paracetamol as active pharmaceutical ingredients, blended with 15.0 g of lactose monohydrate as filler, 2.0 g of microcrystalline cellulose as binder, 0.8 g of croscarmellose sodium as disintegrant, and 0.2 g of magnesium stearate as lubricant. This deliberate reduction in scale ensured cost-effectiveness while maintaining scientific rigor, demonstrating that PAT principles need not rely on industrial resources. The manufacturing sequence employed standard college laboratory equipment across four unit operations: powder blending via mortar and pestle for 5-minute intervals under continuous monitoring by a portable NIR spectrometer (VIAVI Micro NIR); wet granulation using manual agitation in a porcelain dish with distilled water (5 ml) added drop wise until optimal agglomeration (visually confirmed by snowball test); compression of granules into ten 100-mg tablets per batch using a hand-operated single-punch press; and coating application via airbrush spraying of HPMC solution onto tablets tumbling in a glass chamber, with drying accelerated by a laboratory heat gun. Crucially, accessible PAT tools were integrated throughout: the handheld NIR spectrometer tracked blend homogeneity through spectral variance analysis during mixing and measured granule moisture content post-agglomeration, while a portable Raman spectrometer (B&W Teki-Raman) quantified coating thickness development in real-time. Principal Component Analysis (PCA) detected blending endpoints when spectral variance fell below 5% RSD, replacing subjective visual assessment. Partial Least Squares (PLS) regression models calibrated with just 15 spectra predicted moisture content ($R^2 = 0.94$) and coating thickness ($R^2 = 0.91$) using reference data from Karl Fischer titration and digital micrometry. This integration of low-cost hardware and open-source software proved pivotal in overcoming budget limitations typical of academic settings. Results demonstrated significant quality improvements across all processes. PAT-guided blending reduced processing time by 30% (5 minutes versus 7 minutes in control batches) while enhancing content uniformity (RSD of 2.1% vs. 4.8% without PAT). Real-time moisture control during granulation maintained optimal water content (8.5–9.5% w/w), eliminating overwetting issues that previously caused variable tablet hardness. Compression under PAT feedback yielded consistent tablet hardness (5.5 ± 0.3 kg/cm²), and Raman-monitored coating achieved film uniformity with just 3.2% RSD variation a 62% improvement over manually controlled batches (8.7% RSD). Statistical validation via paired t-tests confirmed all enhancements were significant ($p < 0.05$), with effect sizes underscoring PAT's reliability even at micro-scale. Beyond technical outcomes, this project established a pedagogical framework for PAT education. The entire workflow – spanning pre-formulation characterization (solubility testing, FTIR verification), manufacturing, and quality control – was completed in eight 3-hour laboratory sessions using sub-₹10,000 worth of consumables. Students gained hands-on experience in multivariate data analysis, real-time process control, and regulatory-aligned documentation (ICH Q8-Q10), bridging theoretical knowledge and practical skills. The micro-batch approach (producing only 10 tablets per run) minimized waste while maximizing learning iterations, proving that rigorous quality assurance is achievable without industrial infrastructure. By leveraging portable instrumentation, free software, and gram-scale batches, the study achieved industrial-level quality metrics including RTRT-aligned real-time release within typical college constraints. The 20g batch protocol reduces material costs by 95% compared to traditional methods, making PAT training accessible globally. Future work should explore machine learning refinements to chemo metric models and applications in continuous micro-manufacturing. This project ultimately provides a scalable blueprint for integrating modern pharmaceutical engineering principles into curricula, empowering the next generation of scientists to advance Quality by Design in resource-limited settings.

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