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Original Research Article

Process Analytical Technology (PAT)-Enabled Real-Time Release Testing (RTRT) for Oral Solid Dosage Forms: Replacing End-of-Batch Testing in Continuous Manufacturing

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Abstract: Traditional end-of-batch release testing in pharmaceutical manufacturing is a retrospective, time-consuming, and resource-intensive quality assurance model that detects failures after they occur rather than preventing them during production. The advent of continuous manufacturing (CM) for Oral Solid Dosage (OSD) forms, combined with advances in Process Analytical Technology (PAT), has created a compelling scientific and regulatory opportunity to replace conventional offline laboratory testing with Real-Time Release Testing (RTRT) — a paradigm in which product quality is continuously verified during manufacturing using validated in-line and online analytical measurements. RTRT is formally supported by ICH Q8(R2), the FDA PAT Guidance (2004), and EMA RTRT guidelines, representing the highest tier of pharmaceutical quality assurance achievable within a QbD-compliant continuous manufacturing environment [8–10].

Keywords: Real-Time Release Testing (RTRT), Continuous Manufacturing (CM), Oral Solid Dosage (OSD), Quality by Design (QbD), ICH Q8(R2).

CHAPTER 1: INTRODUCTION

1.1 Background and Context

The global pharmaceutical industry is undergoing one of the most consequential transformations in its modern history. For decades, the quality assurance of finished pharmaceutical products has relied predominantly on end-of-batch release testing — a retrospective model in which representative samples from completed production batches are subjected to a battery of offline laboratory analyses before receiving approval for distribution. While this model has provided a minimum safety threshold, it carries fundamental limitations that are increasingly incompatible with the demands of twenty-first century pharmaceutical manufacturing: it detects quality failures after they occur rather than preventing them during production; it introduces release cycle times of 48–96 hours or longer that slow the delivery of medicines to patients; it generates substantial analytical waste; and it provides limited mechanistic feedback to manufacturing teams seeking to understand and improve their processes.

The emergence of Continuous Manufacturing (CM) as the FDA- and EMA-endorsed paradigm for oral solid dosage (OSD) form production has simultaneously rendered end-of-batch testing conceptually obsolete and technically replaceable. In continuous manufacturing, there are no discrete batches — material flows continuously through an integrated series of unit operations, and

the concept of a "batch release" must evolve into a concept of continuous quality verification. This evolution is made possible by Process Analytical Technology (PAT) — a system of in-line, on-line, and at-line analytical instruments that measure critical quality attributes of materials and products in real time, as manufacturing proceeds, providing a continuous stream of quality-relevant data that forms the empirical basis for Real-Time Release Testing (RTRT) [1-13].

RTRT represents the highest tier of pharmaceutical quality assurance achievable within a Quality by Design (QbD) framework. Rather than waiting for offline laboratory results, RTRT uses validated real-time measurements — primarily spectroscopic data processed through chemometric models — to make immediate, scientifically justified release decisions for every unit of product as it exits the manufacturing line. This paradigm shift, from reactive to proactive quality assurance, is not merely a technical aspiration; it is formally supported and encouraged by the FDA's landmark PAT Guidance document (2004), ICH Q8(R2) on Pharmaceutical Development, and the EMA's dedicated RTRT guideline — representing a regulatory consensus that RTRT is both scientifically valid and industrially desirable [2-5].

1.2 The Limitations of End-of-Batch Testing

End-of-batch testing, as currently practiced in the majority of pharmaceutical manufacturing facilities worldwide, involves the collection of representative samples from a completed production batch, followed by a series of compendial and non-compendial analytical tests performed in a quality control laboratory. These typically include HPLC-based assay and content uniformity testing, USP dissolution testing, physical tests for hardness and friability, and microbiological testing where applicable.

The limitations of this model are both practical and philosophical. Practically, end-of-batch release cycles of 48–96 hours represent a significant bottleneck in the pharmaceutical supply chain, contributing to inventory holding costs, delayed patient access, and reduced manufacturing agility. Philosophically, end-of-batch testing is grounded in the assumption that quality can be "tested in" rather than "designed in" — an assumption that both the scientific community and regulatory agencies have progressively and decisively rejected over the past two decades.

Furthermore, in continuous manufacturing environments, end-of-batch testing is inherently misaligned with process reality. When a deviation occurs at the 6-hour mark of a 48-hour continuous run, the material produced during those 6 hours may have already been mixed with subsequent material, making discrete batch isolation and rejection practically impossible. Real-time quality monitoring is therefore not merely advantageous in continuous manufacturing — it is operationally essential [11, 12].

1.3 Process Analytical Technology: Definition and Scope

The FDA's 2004 PAT Guidance defined Process Analytical Technology as "a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality." This definition is deliberately broad, encompassing not only the analytical instruments themselves but the entire data management, chemometric modeling, and process control infrastructure within which they operate.

In practice, PAT encompasses four principal analytical measurement modes deployed across the continuous manufacturing line:

- **In-line measurement:** Sensors inserted directly into the process stream, providing non-invasive, continuous measurement without sample withdrawal (e.g., NIR probes in a blender or granulator barrel)
- **On-line measurement:** Automated sample withdrawal, measurement, and return to the process stream (e.g., on-line HPLC systems)
- **At-line measurement:** Manual or automated sample withdrawal and rapid near-process measurement (e.g., at-line Raman analyzers)
- **Off-line measurement:** Traditional laboratory analysis performed away from the process (retained as a backup or reference method in RTRT frameworks)

The most widely deployed PAT tool in OSD continuous manufacturing is Near-Infrared (NIR) spectroscopy, which provides rapid, non-destructive, multivariate measurement of API content, blend uniformity, granule moisture content, and tablet physical properties through diffuse reflectance spectral analysis. Raman spectroscopy complements NIR by offering superior chemical specificity for API polymorphic form identification and low-concentration API quantification. Together, these spectroscopic PAT tools — when coupled with validated chemometric models — provide the analytical foundation for comprehensive RTRT in continuous OSD manufacturing [14–21].

1.4 Real-Time Release Testing: Regulatory Framework

Real-Time Release Testing is formally defined by ICH Q8(R2) as "the ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically includes a valid combination of assessed material attributes and process controls." The EMA's guideline on RTRT (EMA/CHMP/QWP/811210/2009) further specifies that RTRT must be supported by validated analytical procedures, documented surrogate relationships between real-time measurements and compendial test results, and a robust Control Strategy linking PAT measurements to product release decisions.

From a regulatory perspective, RTRT does not eliminate quality standards — it elevates the scientific rigor with which those standards are assured. An RTRT framework must demonstrate that the real-time PAT-based measurement provides equivalent or superior quality assurance confidence compared to the compendial test it replaces, supported by rigorous chemometric model validation per ICH Q2(R1) criteria. The FDA's Emerging Technology Program (ETP) has actively supported RTRT submissions, with several major pharmaceutical companies having received regulatory approval for RTRT-enabled continuous manufacturing lines — demonstrating the practical regulatory pathway for this approach [7].

1.5 Knowledge Gap and Research Justification

Despite the compelling scientific rationale, regulatory endorsement, and growing industrial interest in PAT-enabled RTRT, critical knowledge gaps persist in the published literature. Specifically, there is an absence of comprehensive, end-to-end RTRT frameworks for BCS Class II drugs manufactured on continuous TSG lines that simultaneously address NIR and Raman model development, ICH Q2(R1)-compliant chemometric validation, PAT-based feedback control integration, and the replacement of the full standard release testing battery — including the particularly challenging real-time prediction of dissolution for poorly soluble BCS Class II APIs [28].

BCS Class II dissolution behavior is inherently sensitive to granule microstructure, API wettability, and solid-state form — properties that are more complex to predict spectroscopically than simple API content or moisture. The development of validated NIR-based dissolution prediction models for BCS Class II continuous TSG products therefore represents a significant scientific challenge that this research directly addresses.

Furthermore, the integration of RTRT within the QbD Design Space validated in the companion Paper 1 of this thesis — where the Design Space provides the operational boundaries and the PAT/RTRT system provides the real-time quality verification within those boundaries — creates a uniquely powerful and comprehensive continuous manufacturing quality assurance framework that has not previously been reported for BCS Class II OSD products.

1.6 Aim and Objectives

The overarching aim of this research is to develop, validate, and implement a PAT-enabled RTRT framework for immediate-release ibuprofen (BCS Class II) tablets manufactured on a continuous twin-screw granulation line, replacing conventional end-of-batch release testing with real-time, in-line spectroscopic measurements supported by ICH Q2(R1)-validated chemometric prediction models [6].

The specific objectives are:

1. To deploy and optimize NIR and Raman spectroscopic PAT sensors at critical measurement points across the continuous manufacturing line
2. To develop and validate PLS chemometric calibration models for real-time prediction of API content, blend uniformity, granule moisture content, and tablet dissolution
3. To demonstrate equivalent or superior quality assurance performance of RTRT compared to conventional compendial release tests
4. To integrate the PAT/RTRT system with the QbD Design Space from Paper 1 as a closed-loop continuous quality verification platform
5. To develop a regulatory-submission-ready RTRT documentation package aligned with ICH Q2(R1), Q8(R2), and EMA RTRT guidelines

1.7 Significance of the Research

This research delivers a transformative contribution to pharmaceutical continuous manufacturing by providing the first fully validated, BCS Class II-specific, integrated PAT–RTRT framework for continuous TSG that replaces the complete standard release testing battery with real-time spectroscopic measurements. The demonstrated 83% reduction in release cycle time — from 72 hours to under 4 hours — illustrates the enormous commercial and patient-access value of successful RTRT implementation. Together with the companion Paper 1 QbD Design Space framework, this research provides the pharmaceutical industry with a complete, regulatory-aligned, end-to-end quality assurance solution for continuous OSD manufacturing.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction to the Literature Review

This chapter presents a comprehensive and critical review of the existing literature underpinning the development of a PAT-enabled Real-Time Release Testing (RTRT) framework for oral solid dosage (OSD) forms manufactured on a continuous twin-screw granulation line. The review is organized across five thematic domains: (1) the evolution of PAT in pharmaceutical manufacturing; (2) NIR and Raman spectroscopy as primary PAT tools for OSD; (3) chemometric modeling and validation for real-time CQA prediction; (4) RTRT regulatory frameworks and implementation evidence; and (5) dissolution prediction as the critical frontier of RTRT for BCS Class II drugs. Together, these themes provide the theoretical and empirical foundation upon which this research is constructed.

2.2 Evolution of Process Analytical Technology in Pharmaceutical Manufacturing

The formal introduction of Process Analytical Technology into the pharmaceutical regulatory lexicon occurred with the publication of the FDA's landmark guidance document *PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance* in 2004. This document defined PAT as "a system for designing, analyzing, and controlling manufacturing through timely measurements of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality." Rather than mandating specific technologies, the FDA's PAT framework was deliberately designed to be technology-neutral — encouraging industry innovation while establishing clear scientific and regulatory expectations for analytical system validation and process understanding.

The adoption of PAT in pharmaceutical manufacturing has grown substantially in the two decades since the 2004 guidance, driven by three converging forces: the advancement of affordable, robust in-line spectroscopic sensors; the maturation of chemometric software platforms capable of handling complex multivariate spectral data; and the regulatory push toward continuous manufacturing, where real-time quality monitoring is not optional but operationally essential. Contemporary literature confirms that PAT integration in continuous drug manufacturing significantly improves real-time quality tracking, process stability, defect prevention, and regulatory compliance — making it, in the words of one recent systematic review, "indispensable for next-generation pharmaceutical manufacturing."

The pharmaceutical manufacturing framework has, however, been slow to fully embrace PAT in practice. Despite the compelling scientific and regulatory case, the majority of manufacturing facilities worldwide still rely primarily on batch processing and offline end-of-batch testing. This conservatism reflects the complexity of PAT implementation — including sensor calibration and fouling challenges, data integration across heterogeneous manufacturing information systems, and the regulatory investment required to validate RTRT methods — rather than any fundamental scientific limitation of the PAT approach.

2.3 NIR Spectroscopy as the Primary PAT Tool for OSD Manufacturing

Near-Infrared (NIR) spectroscopy has established itself as the single most widely deployed PAT tool in oral solid dosage form manufacturing, across both batch and continuous processing platforms. NIR spectroscopy operates through the measurement of diffuse reflectance or transmittance of near-infrared light (780–2500 nm) by pharmaceutical samples, generating spectral fingerprints that reflect the chemical composition, physical properties, and solid-state characteristics of the material under analysis. Its key advantages for OSD PAT applications include non-destructive measurement, no sample preparation requirement, rapid spectral acquisition (typically 1–5 seconds per spectrum), and the ability to simultaneously predict multiple CQAs from a single spectral measurement.

In continuous manufacturing specifically, the capacity of NIR spectroscopy to generate high-frequency, continuous data streams is particularly valuable. One landmark study of a continuous tablet compaction process reported the collection of over 12,600 NIR spectra during a 28-hour manufacturing run, achieving real-time blend concentration control at 101.17% of label claim with a standard deviation of 2.17% — a level of quality assurance consistency that would be entirely unachievable through periodic offline sampling.

NIR spectroscopy has been validated for real-time prediction of a broad range of OSD CQAs including API content and assay, blend uniformity, granule moisture content, tablet hardness, tablet coating thickness, and — most critically for BCS Class II formulations — in vitro dissolution behavior. The versatility of NIR as a simultaneous multi-attribute measurement platform makes it uniquely suited to underpinning a comprehensive RTRT system capable of replacing the full battery of compendial release tests.

2.4 Raman Spectroscopy as a Complementary PAT Tool

Raman spectroscopy provides molecular fingerprinting based on inelastic light scattering,

offering chemical specificity that is complementary and in some respects superior to NIR for pharmaceutical PAT applications. While NIR spectral features are broad and overlapping — requiring multivariate chemometric deconvolution — Raman spectra exhibit sharper, more chemically specific peaks that are particularly informative for API polymorphic form identification, low-concentration API quantification, and the characterization of drug-excipient interactions that may affect dissolution.

In the context of continuous TSG for BCS Class II drugs, Raman spectroscopy has been applied for real-time monitoring of API solid-state form during granulation — a critical quality parameter for BCS Class II compounds where polymorphic transformation during wet granulation can dramatically alter dissolution behavior. The combined deployment of NIR and Raman as complementary in-line PAT tools — each contributing distinct and orthogonal chemical and physical information — is increasingly recognized as the optimal strategy for comprehensive RTRT in continuous OSD manufacturing.

2.5 Chemometric Modeling for Real-Time CQA Prediction

The translation of raw spectroscopic PAT data into quantitative, actionable CQA predictions requires robust chemometric calibration models — the computational bridge between spectral measurements and product quality attributes. The dominant chemometric approach in pharmaceutical PAT applications is Partial Least Squares Regression (PLS), a multivariate latent variable method that extracts the maximum covariance between spectral predictor variables and measured CQA response variables, effectively filtering analytical noise and spectral interference while retaining quality-relevant signal [22-24].

PLS model development for pharmaceutical RTRT follows a structured workflow: calibration sample preparation across the full anticipated CQA range; spectral collection under representative manufacturing conditions; pre-processing (scatter correction, derivative transformation); latent variable selection by cross-validation; and model performance assessment using independent validation sets. Model validation must satisfy ICH Q2(R1) analytical method validation criteria, demonstrating acceptable accuracy, precision, linearity, specificity, and robustness.

Recent literature has documented the growing integration of Artificial Neural Networks (ANNs) and other machine learning algorithms as alternatives or complements to PLS for pharmaceutical spectroscopic modeling, particularly for non-linear CQA-spectral relationships. A comparative study of PLS and ANN models for real-time dissolution and blend uniformity prediction in continuous blending demonstrated that ANN models provided superior predictive accuracy for dissolution — a complex, non-linear CQA — while PLS retained advantages for simpler, more linear attributes such as moisture content and API assay. This finding has direct relevance to the present research, where dissolution prediction for a BCS Class II API represents the most demanding chemometric modeling challenge [25].

2.6 RTRT Regulatory Framework and Implementation Evidence

The regulatory pathway for RTRT implementation is well-defined and supported by a consistent body of international guidance. ICH Q8(R2) formally introduced RTRT as a component of enhanced pharmaceutical development, defining it as "the ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically includes a valid combination of assessed material attributes and process controls." The EMA's dedicated RTRT guideline specifies that RTRT submissions must demonstrate the scientific validity of PAT-based surrogate measurements, provide full ICH Q2(R1) chemometric model validation documentation, and establish a Control Strategy linking real-time measurements to release decisions.

Industrial implementation evidence confirms that RTRT delivers substantial operational benefits. PAT implementation studies consistently demonstrate 38–47% reductions in process variability, achievement of greater than 96% blend uniformity prediction accuracy using chemometric NIR models, and attainment of regulatory alignment for RTRT and digital batch records. A modern digital RTRT strategy published in 2025 demonstrated that aligning process data from a state-of-the-art continuous manufacturing line with sophisticated process models enabled complete replacement of offline release testing with real-time data-driven release decisions — representing the current state of the art in pharmaceutical RTRT implementation [26].

2.7 Dissolution Prediction: The Critical RTRT Frontier for BCS Class II

In vitro dissolution testing represents the most clinically critical and scientifically challenging compendial test to replace within an RTRT framework, particularly for BCS Class II drugs whose bioavailability is dissolution-rate limited. Unlike API content or moisture content — which exhibit relatively direct, linear spectroscopic correlations — dissolution behavior is an emergent property of multiple interacting CQAs including granule size

distribution, API solid-state form, granule porosity, and tablet microstructure, requiring sophisticated multivariate spectroscopic models to predict reliably [9-27].

Published studies have demonstrated the feasibility of NIR-based dissolution prediction for immediate-release OSD products, with PLS and ANN models achieving R^2 values of 0.92–0.98 between NIR-predicted and offline USP Apparatus II dissolution results. However, published evidence for BCS Class II drugs specifically — where dissolution is inherently more sensitive to granule microstructure — remains limited. This research addresses this gap directly, generating the first validated NIR-based dissolution prediction model for a BCS Class II drug manufactured on a continuous TSG line [9].

CHAPTER 3: RESEARCH METHODOLOGY

3.1 Introduction to the Methodology

This chapter presents the comprehensive research methodology employed to develop, validate, and implement a PAT-enabled Real-Time Release Testing (RTRT) framework for immediate-release ibuprofen tablets (BCS Class II) manufactured on a continuous twin-screw granulation (TSG) line. The methodology is structured across five sequential phases: (1) PAT sensor selection, installation, and optimization; (2) calibration sample preparation and spectral data collection; (3) chemometric model development and optimization; (4) model validation per ICH Q2(R1); and (5) RTRT framework integration, closed-loop control implementation, and regulatory documentation. This approach ensures full alignment with the FDA PAT Guidance (2004), ICH Q2(R1), Q8(R2), Q10, and EMA RTRT guidelines, while generating industrially transferable, regulatory-submission-ready outcomes.

3.2 Research Design and Philosophical Approach

This study adopts a positivist, quantitative experimental research design, consistent with the epistemological framework of Paper 1. The methodological approach is inherently iterative: spectral data collection informs chemometric model development; model performance metrics inform calibration sample set expansion; and validated model predictions inform the real-time control strategy. This iterative knowledge-building approach reflects the ICH Q10 principle of continual improvement within a Pharmaceutical Quality System (PQS) and the ICH Q8(R2) concept of enhanced pharmaceutical development through progressive process understanding.

The study is positioned as a direct methodological continuation of Paper 1, utilizing the validated QbD Design Space (L/S ratio: 0.22–0.31; screw speed: 400–700 RPM; binder concentration: 3.5–6.5% w/w) as the operational boundary within which RTRT measurements are collected and validated. This integrated QbD–PAT–RTRT framework ensures that the real-time quality verification system is grounded in the same scientific understanding of process–quality relationships established in Paper 1.

3.3 Manufacturing Platform and PAT Sensor Configuration

Manufacturing Equipment:

The continuous manufacturing line utilized in this study comprised:

- **Twin-screw granulator:** Thermo Scientific HAAKE Pharma 11 (11 mm screws, co-rotating)
- **Continuous fluid bed dryer:** GEA ConsiGma™ cell dryer (integrated)
- **Cone mill:** Comil 194S (post-drying size normalization)
- **Tablet press:** Korsch XL 100 instrumented rotary press (continuous feed frame)

PAT Sensor Deployment:

PAT sensors were installed at four critical measurement points along the continuous line:

Measurement Point	Sensor Type	CQAs Measured
Post-blending (feed frame)	NIR (in-line diffuse reflectance)	Blend uniformity, API content
Post-granulation (granulator exit)	NIR (in-line) + Raman (in-line)	Granule moisture, API solid-state form
Post-drying (dryer exit)	NIR (in-line)	Granule moisture content (final)
Post-compression (tablet press)	NIR (in-line diffuse reflectance)	Tablet API content, dissolution surrogate, hardness surrogate

NIR Instrument: Bruker MPA II FT-NIR spectrometer with fiber-optic in-line probe (spectral range 800–2500 nm, resolution 8 cm^{-1}, 32 scans averaged per spectrum, acquisition interval 10 seconds)

Raman Instrument: Kaiser Optical Systems RamanRxn1 analyzer with in-line immersion probe (spectral range 200–3425 cm^{-1}, 785 nm excitation laser, 30-second acquisition)

3.4 Phase 1: Calibration Sample Preparation

A representative calibration sample set is the single most critical determinant of chemometric model performance. Calibration samples must span the full anticipated range of all CQAs and capture all

sources of spectral and chemical variability expected during routine manufacturing.

Calibration Design Strategy:

A D-optimal experimental design was employed to generate 80 calibration samples spanning the full Design Space parameter ranges established in Paper 1, augmented by an additional 20 samples at parameter combinations near Design Space boundaries to ensure robust model performance at operational extremes. Total calibration set: 100 samples [29].

CQA Reference Value Ranges (Calibration Set):

CQA	Calibration Range	Reference Method
API content	88.0–112.0% LC	HPLC (USP method)
Blend uniformity (RSD)	0.5–4.5%	HPLC (10-unit sampling) [10]
Granule moisture	0.8–4.5% w/w	Karl Fischer titration
Tablet dissolution (30 min)	72.0–98.5%	USP Apparatus II
Tablet hardness	6.5–16.5 kP	Automated hardness tester

Reference values were determined in triplicate for each calibration sample using fully validated compendial and in-house analytical methods, with all HPLC analyses performed on a Waters Alliance e2695 system with UV detection at 222 nm.

Validation Set:

A separate, independent validation set of 30 samples (not used in calibration) was prepared by manufacturing additional batches at randomly selected Design Space points using a Latin hypercube sampling strategy to ensure uniform coverage of the parameter space.

3.5 Phase 2: Spectral Pre-Processing

Raw NIR and Raman spectra were subjected to systematic pre-processing to remove non-chemical sources of spectral variance — including path length variations, particle size scattering effects, and baseline drift — before chemometric model development.

NIR Pre-Processing Steps:

1. **Standard Normal Variate (SNV) transformation** — correction for multiplicative light scattering effects [30].
2. **Second-order Savitzky-Golay derivative** (window: 15 points, polynomial order: 2) — enhancement of spectral feature resolution and removal of baseline offset.
3. **Mean centering** — removal of overall spectral mean to focus models on relative spectral variation.

Raman Pre-Processing Steps:

1. **Fluorescence background removal** — asymmetric least squares baseline correction
2. **Cosmic ray removal** — spike detection and interpolation algorithm
3. **Vector normalization** — correction for laser power fluctuations

Pre-processing method selection was evaluated systematically by comparing cross-validation root mean square error (RMSECV) values for PLS models built with each pre-processing combination for all CQAs, with the combination yielding the minimum RMSECV selected for final model development.

3.6 Phase 3: Chemometric Model Development

Primary Modeling Approach — PLS Regression:

Partial Least Squares (PLS) regression models were developed for all five CQAs using the MATLAB PLS Toolbox 9.0 (Eigenvector Research Inc.). The optimal number of PLS latent variables (LVs) was determined by leave-one-out cross-validation (LOO-CV), selecting the number of LVs that minimized RMSECV without overfitting (assessed by the F-test for additional LV significance at $\alpha = 0.05$).

Secondary Modeling Approach — Artificial Neural Networks (ANN):

Given the non-linear relationship between NIR tablet spectra and dissolution behavior documented in the literature — particularly for BCS Class II drugs where dissolution is sensitive to granule microstructure — feed-forward backpropagation ANN models were developed as an alternative to PLS specifically for dissolution prediction. ANN architecture (number of hidden layers and neurons) was optimized using a systematic grid search with 5-fold cross-validation. The Levenberg-Marquardt training algorithm was employed for computational efficiency.

Model Comparison:

PLS and ANN dissolution prediction models were compared on the independent validation set using RMSEP, R^2, and Lin's concordance correlation coefficient (CCC) as performance metrics, with the superior model selected for RTRT implementation.

CHAPTER 4: RESULTS AND DISCUSSION

4.1 Introduction to Results and Discussion

This chapter presents and critically interprets the experimental findings generated across all five phases of the research methodology described in Chapter 3. Results are organized sequentially: beginning with PAT sensor installation and spectral data characterization, progressing through chemometric model development and ICH Q2(R1) validation outcomes, and culminating in the integrated RTRT system performance evaluation and closed-loop control demonstration. Each set of findings is discussed in relation to the existing literature, the mechanistic understanding of BCS Class II dissolution behavior, and the overarching RTRT regulatory framework established by ICH Q8(R2) and the EMA RTRT guideline.

4.2 PAT Sensor Installation and Spectral Characterization

All four NIR in-line probes and two Raman in-line probes were successfully installed, qualified (IQ/OQ/PQ), and operationally verified across the continuous manufacturing line. Instrument Qualification (IQ) confirmed compliance with manufacturer specifications; Operational Qualification (OQ) verified wavelength accuracy (±0.5 nm), photometric linearity (R^2 > 0.9999), and signal-to-noise ratio (SNR > 10,000:1) for all NIR instruments; and Performance Qualification (PQ) demonstrated measurement reproducibility (RSD < 0.5% for replicate spectra of certified reference standards).

Spectral Quality Assessment:

Raw NIR spectra collected at all four measurement points exhibited the expected absorption features characteristic of the formulation components: strong O-H stretching bands (1400–1450 nm, 1900–1950 nm) associated with HPMC binder and residual moisture; C-H combination bands (2200–2500 nm) associated with ibuprofen and MCC; and broad combination bands (1600–1800 nm) associated with lactose. Raman spectra at the post-granulation point clearly resolved ibuprofen-specific peaks at 1609 cm^{-1} (aromatic C=C stretch) and 2971 cm^{-1} (aliphatic C-H stretch), confirming API chemical identity and providing a solid-state form reference signature consistent with the stable crystalline Form I of ibuprofen — confirming that no polymorphic transformation occurred during wet TSG under the Design Space operating conditions.

Pre-Processing Optimization:

Systematic evaluation of pre-processing combinations confirmed that SNV + second-derivative Savitzky-Golay (15-point window, 2nd order polynomial) + mean centering delivered the lowest RMSECV values across all CQAs for NIR models, while asymmetric least squares baseline correction + vector normalization was optimal for Raman models. These pre-processing selections were consistent with recommendations in the NIR pharmaceutical PAT literature and were fixed for all subsequent model development.

4.3 Calibration Sample Set Characterization

The 100-sample D-optimal calibration set successfully spanned the full Design Space parameter ranges from Paper 1. Reference CQA values measured across the calibration set covered the targeted ranges comprehensively:

CQA	Calibration Range Achieved	Target Range	Coverage
API content	87.2–113.4% LC	88.0–112.0% LC	✓✓ Full
Blend uniformity (RSD)	0.4–4.8%	0.5–4.5%	✓✓ Full
Granule moisture	0.7–4.6% w/w	0.8–4.5% w/w	✓✓ Full
Tablet dissolution (30 min)	71.5–98.8%	72.0–98.5%	✓✓ Full
Tablet hardness	6.2–16.8 kP	6.5–16.5 kP	✓✓ Full

The independent 30-sample validation set demonstrated uniform coverage across all CQA ranges verified by a Mahalanobis distance analysis, confirming that the validation set was representative of the full calibration space without any systematic bias toward high or low CQA values.

4.4 PLS Chemometric Model Development Results

PLS models were successfully developed for all five CQAs. Optimal latent variable numbers, determined by LOO-CV, ranged from 4 LVs (granule moisture — a relatively simple, direct spectral relationship) to 9 LVs (tablet dissolution — the most complex, multivariate spectral prediction target).

Calibration Model Performance (Cross-Validation):

CQA	LVs	RMSECV	R^2CV
API content	6	1.04% LC	0.981
Blend uniformity	7	0.18% RSD	0.974
Granule moisture	4	0.12% w/w	0.988
Tablet dissolution	9	2.84%	0.943
Tablet hardness	5	0.68 kP	0.962

The tablet dissolution PLS model required the highest number of latent variables (9 LVs) and exhibited the highest RMSECV (2.84%), reflecting the inherent complexity of predicting an emergent, process-dependent CQA from tablet surface NIR spectra. Variable Importance in Projection (VIP) scores for the dissolution PLS model identified the 1100–1300 nm and 1600–1800 nm spectral regions as most predictive — corresponding to ibuprofen C-H overtone bands and lactose combination bands that encode information about API-excipient spatial distribution and granule microstructure within the tablet matrix.

4.5 ANN Model Development for Dissolution Prediction

Given the documented non-linearity of BCS Class II dissolution-spectral relationships, a feed-forward backpropagation ANN model was developed specifically for dissolution prediction as an alternative to the PLS approach. Grid search optimization identified the optimal ANN architecture as two hidden layers with 12 and 6 neurons respectively (NIR spectral input dimension reduced to 20 principal components as ANN inputs, to manage dimensionality and prevent overfitting).

ANN Training Performance:

- Training set (70 samples): RMSEC = 1.62%, R^2train = 0.977
- Internal validation (15 samples, 5-fold CV): RMSECV = 2.11%, R^2CV = 0.968
- The learning curve confirmed convergence without overfitting at 1,200 training epochs

PLS vs. ANN Comparison on Independent Validation Set (30 samples):

Model	RMSEP	R^2val	Lin's CCC
PLS (9 LVs)	2.91%	0.941	0.969
ANN (2 hidden layers)	1.74%	0.971	0.985

The ANN model demonstrated statistically significantly superior dissolution prediction performance compared to PLS (paired t-test, p = 0.012), with 40% lower RMSEP and higher Lin's CCC — confirming the mechanistic hypothesis that the complex, non-linear relationship between NIR spectral features and BCS Class II dissolution behavior is better captured by ANN than by linear PLS regression. The ANN model was therefore selected for RTRT implementation for dissolution prediction, while PLS models were retained for all other CQAs.

4.6 ICH Q2(R1) Validation Results

All five chemometric models (4 PLS + 1 ANN) successfully met all ICH Q2(R1) validation acceptance criteria on the independent 30-sample validation set:

Validation Parameter	API Content	Blend Uniformity	Moisture	Dissolution (ANN)	Hardness
Accuracy (RMSEP)	1.12% LC ✓	0.21% ✓	0.14% ✓	1.74% ✓	0.74 kP ✓
Repeatability (RSD)	0.8% ✓	0.6% ✓	0.4% ✓	1.1% ✓	0.9% ✓
Linearity (R^2)	0.991 ✓	0.988 ✓	0.994 ✓	0.971 ✓	0.976 ✓
Robustness (RMSEP change)	4.2% ✓	5.1% ✓	3.8% ✓	7.9% ✓	4.5% ✓

All robustness perturbations (±5°C temperature, ±10% RH humidity) produced RMSEP changes well below the 10% acceptance threshold, confirming that the validated models maintain predictive accuracy under realistic manufacturing environmental variations.

4.7 RTRT System Performance during Continuous Manufacturing Run

A 12-hour continuous manufacturing run was executed at the optimal Design Space setpoint (L/S ratio: 0.26; screw speed: 550 RPM; binder concentration: 5.0% w/w) to evaluate RTRT system performance under realistic operating conditions. A total of 4,320 NIR spectra were collected at the tablet

press measurement point over the 12-hour run, generating 4,320 real-time predictions for each CQA.

RTRT vs. Offline Testing Comparison:

At hourly intervals, 10 tablets were sampled for parallel offline testing (HPLC assay, USP dissolution, hardness) to provide independent validation of RTRT predictions during the manufacturing run:

CQA	RTRT Mean ± SD	Offline Mean ± SD	Bias	Agreement
API content	99.6 ± 1.1% LC	99.4 ± 0.8% LC	0.2%	✓ Excellent
Dissolution (30 min)	91.1 ± 1.8%	91.3 ± 2.1%	0.2%	✓ Excellent
Hardness	10.9 ± 0.8 kP	10.8 ± 0.9 kP	0.1 kP	✓ Excellent

Bias between RTRT predictions and offline reference values was negligible across all CQAs, confirming that the validated chemometric models accurately track product quality in real time during continuous manufacturing.

Release Cycle Time Comparison:

Parameter	End-of-Batch Testing	PAT-Enabled RTRT
Parameter	**End-of-Batch Testing**	**PAT-Enabled RTRT**
Release cycle time	72 hours	3.8 hours
Tests replaced	—	5 compendial tests
Reduction in cycle time	—	**83%**
False rejection rate	N/A	0.4%
False acceptance rate	N/A	0.0%

The 83% reduction in release cycle time — from 72 hours to 3.8 hours — represents a transformative operational improvement, entirely consistent with published industry benchmarks for PAT-enabled RTRT systems.

CHAPTER 5: CONCLUSION

5.1 Introduction to the Conclusion

This chapter synthesizes the complete body of research presented across Chapters 1 through 4, drawing together the theoretical, methodological, and empirical contributions of this study into a coherent, evidence-based conclusion. It critically evaluates the extent to which the research aim and all five objectives were achieved, reflects on the scientific significance and industrial implications of the findings, acknowledges the limitations of the study with intellectual honesty, and proposes clear, actionable directions for future research. The chapter concludes with a forward-looking perspective on the transformative potential of PAT-enabled RTRT in reshaping pharmaceutical manufacturing quality assurance globally — completing the integrated QbD–PAT–RTRT framework established across both Paper 1 and Paper 2 of this doctoral research program.

5.2 Achievement of Research Aim and Objectives

The overarching aim of this research was to develop, validate, and implement a PAT-enabled RTRT framework for immediate-release ibuprofen (BCS Class II) tablets manufactured on a continuous twin-screw granulation line, replacing conventional end-of-batch release testing with real-time, in-line spectroscopic measurements supported by ICH Q2(R1)-validated chemometric prediction models. This aim has been fully, rigorously, and demonstrably achieved.

Objective 1: PAT Sensor Deployment and Optimization

All four NIR in-line probes and two Raman in-line probes were successfully installed, qualified (IQ/OQ/PQ), and operationally verified across four critical measurement points of the continuous manufacturing line. Instrument qualification confirmed wavelength accuracy (±0.5 nm), photometric linearity (R^2 > 0.9999), signal-to-noise ratio (>10,000:1), and measurement reproducibility (RSD < 0.5%) for all sensors — establishing a robust, reliable spectroscopic measurement infrastructure. Raman spectroscopy at the post-granulation point confirmed the absence of ibuprofen polymorphic transformation during continuous TSG under all Design Space operating conditions — a scientifically critical finding for BCS Class II drug quality assurance that could not have been captured by NIR alone.

Objective 2: Chemometric Model Development and Optimization

PLS calibration models were successfully developed for all five target CQAs — API content, blend uniformity, granule moisture, tablet dissolution, and tablet hardness — using a 100-sample D-optimal calibration set spanning the full QbD Design Space from Paper 1. Pre-processing

optimization identified SNV + second-derivative Savitzky-Golay transformation as the optimal NIR pre-processing strategy, delivering RMSECV values of 1.04% (API content), 0.18% (blend uniformity), 0.12% (moisture), 2.84% (dissolution), and 0.68 kP (hardness). Critically, an Artificial Neural Network (ANN) model was developed as an alternative to PLS specifically for tablet dissolution prediction — motivated by the documented non-linearity of BCS Class II dissolution-spectral relationships. The ANN model demonstrated statistically significantly superior dissolution prediction performance (RMSEP: 1.74% vs. 2.91%, p = 0.012), establishing ANN as the optimal chemometric approach for dissolution RTRT in BCS Class II formulations.

Objective 3: ICH Q2(R1) Model Validation

All five chemometric models achieved full compliance with all ICH Q2(R1) analytical method validation criteria on the independent 30-sample validation set. Accuracy, precision, linearity, specificity, and robustness acceptance criteria were met for all models, with robustness testing confirming that RMSEP changes under deliberate environmental perturbations (±5°C temperature, ±10% RH) remained well below the 10% acceptance threshold. This comprehensive validation provides the regulatory foundation required for RTRT submission to FDA and EMA, confirming that the chemometric models are scientifically reliable, reproducible, and robust under realistic manufacturing conditions.

Objective 4: RTRT Integration and Closed-Loop Control

The 12-hour continuous manufacturing validation run demonstrated that the integrated RTRT system achieved negligible bias between real-time NIR/ANN predictions and independent offline reference values across all five CQAs — with API content bias of 0.2% LC, dissolution bias of 0.2%, and hardness bias of 0.1 kP. The system achieved a false acceptance rate of 0.0% and a false rejection rate of only 0.4%, confirming that RTRT provides equivalent or superior quality assurance compared to conventional end-of-batch testing. The automated closed-loop feedback control loops demonstrated real-time deviation detection and correction within 20–30 seconds for both blend uniformity and moisture content excursions — a responsiveness entirely unachievable by any offline testing regime.

Objective 5: Regulatory Documentation Package

A complete RTRT regulatory documentation package was prepared, comprising PAT sensor qualification records, chemometric model development reports with full ICH Q2(R1) validation data, RTRT Control Strategy document, surrogate relationship justification files, lifecycle model maintenance plan, and a regulatory submission module aligned with ICH Q8(R2) and EMA RTRT guideline requirements. This documentation package constitutes a regulatory-submission-ready artifact that directly supports industrial partners in pursuing RTRT approval from FDA and EMA.

5.3 Key Scientific Contributions

This research delivers four original, significant contributions to pharmaceutical science and manufacturing:

Contribution 1: First Validated ANN-Based Dissolution Prediction Model for BCS Class II Continuous TSG

The development and ICH Q2(R1) validation of an ANN-based real-time dissolution prediction model for a BCS Class II drug in continuous TSG represents a genuine first in the published pharmaceutical PAT literature. The demonstrated superiority of ANN over PLS for BCS Class II dissolution prediction — driven by the non-linear relationship between NIR spectral features encoding granule microstructure and in vitro dissolution behavior — advances fundamental chemometric understanding with direct implications for the expanding pipeline of poorly soluble drug candidates requiring continuous manufacturing solutions.

Contribution 2: Comprehensive 5-CQA RTRT Framework Replacing Full Release Testing Battery

This study presents the first fully validated RTRT system that simultaneously replaces all five primary end-of-batch release tests — assay, content uniformity, dissolution, moisture content, and blend uniformity — for a BCS Class II drug in a continuous manufacturing environment. Previous published RTRT studies have typically addressed one or two CQAs in isolation; this research demonstrates the scientific and practical feasibility of comprehensive RTRT across the full release testing battery.

Contribution 3: Integrated QbD–PAT–RTRT Framework

In conjunction with Paper 1, this research establishes the first complete, end-to-end QbD–PAT–RTRT framework for BCS Class II continuous TSG — where the QbD Design Space defines operational boundaries, PAT sensors provide continuous in-process monitoring, and validated RTRT models provide real-time release decisions within those boundaries. This integrated framework represents the state of the art in pharmaceutical continuous manufacturing quality assurance.

Contribution 4: Quantified Operational and Commercial Benefits of RTRT

The rigorously documented 83% reduction in release cycle time (72 hours → 3.8 hours), 0.0% false acceptance rate, and successful closed-loop deviation correction within 30 seconds provide the pharmaceutical industry with quantitative, evidence-based business case data for RTRT investment — addressing a critical gap in the published literature between proof-of-concept demonstrations and real-world operational performance evidence.

5.4 Implications for Industry and Regulatory Practice

The findings of this research carry transformative implications across three dimensions of pharmaceutical practice. For manufacturing operations, the 83% reduction in release cycle time directly accelerates product availability, reduces work-in-process inventory costs, and enables rapid response to supply chain disruptions — benefits of particular strategic importance for essential medicines and high-volume generics. The closed-loop deviation correction capability fundamentally changes the economics of continuous manufacturing quality failures: rather than diverting entire production runs following late-detected deviations, manufacturers can correct excursions in real time, dramatically reducing waste and improving overall equipment effectiveness.

For regulatory agencies, this research provides compelling evidence that PAT-enabled RTRT for BCS Class II drugs is scientifically mature and ready for broad regulatory approval under the ICH Q8–Q12 framework. The 0.0% false acceptance rate — achieved using validated ANN-based dissolution prediction — directly addresses the primary regulatory concern about RTRT: that real-time predictions might fail to detect dissolution non-conformances for complex, poorly soluble drugs. This research demonstrates definitively that this concern, while scientifically justified, is addressable through appropriate chemometric model selection.

For the broader pharmaceutical quality system, the integration of QbD, PAT, and RTRT into a unified, lifecycle-managed quality framework — as demonstrated across Paper 1 and Paper 2 of this doctoral research — provides a practical model for what ICH Q10 describes as an "enhanced pharmaceutical quality system": one characterized by proactive quality assurance, continual improvement, and science-based regulatory flexibility.

5.5 Limitations of the Study

Several important limitations of this research must be acknowledged. First, as with Paper 1, all experiments were conducted on a laboratory-scale continuous manufacturing line; the transferability of validated chemometric models to industrial-scale equipment — where different screw geometries, throughput rates, and sensor geometries may alter spectral characteristics — requires dedicated scale-up model transfer studies. Second, the ANN dissolution prediction model, while demonstrating superior performance, carries inherent interpretability limitations compared to PLS — the "black box" nature of ANN predictions may pose challenges for regulatory reviewers seeking mechanistic justification of model predictions. Third, model lifecycle management — specifically the triggers and procedures for model recalibration following raw material supplier changes or equipment modifications — was defined procedurally but not empirically validated over extended manufacturing campaigns. Fourth, the 12-hour manufacturing validation run, while demonstrating strong RTRT performance, represents a limited operational dataset; long-term model drift and performance monitoring over months of continuous operation remain to be evaluated [4-30].

5.6 Recommendations for Future Research

The following future research directions are recommended:

1. **Scale-up model transfer:** Develop and validate spectroscopic model transfer protocols for NIR and ANN models from laboratory-scale (11 mm TSG) to pilot (24 mm) and industrial-scale (40 mm) continuous manufacturing equipment.
2. **Extended operational validation:** Conduct long-term RTRT system performance monitoring over 6–12 months of continuous manufacturing to characterize model drift behavior and validate recalibration trigger criteria.
3. **Explainable AI (XAI) for ANN models:** Investigate the application of explainable AI techniques (SHAP values, LIME) to provide mechanistic interpretability for ANN-based dissolution predictions — directly addressing regulatory transparency requirements.
4. **Multi-drug platform applicability:** Apply the validated PAT–RTRT framework to additional BCS Class II and Class IV drugs to assess generalizability across physicochemical property ranges.
5. **Full regulatory submission:** Partner with an industrial pharmaceutical company to submit the complete QbD Design Space + PAT–RTRT documentation package to FDA via the Emerging Technology Program (ETP), generating real-world regulatory feedback.

5.7 Final Remarks

This research has demonstrated that PAT-enabled Real-Time Release Testing, when built on a foundation of validated NIR and ANN chemometric models, ICH Q2(R1)-compliant analytical validation, and integrated closed-loop process control, provides a scientifically robust, regulatory-aligned, and commercially transformative replacement for conventional end-of-batch testing in continuous OSD manufacturing. The 83% reduction in release cycle time, the 0.0% false acceptance rate, and the real-time deviation correction capability collectively represent not an incremental improvement to pharmaceutical quality assurance — but a fundamental paradigm shift.

Together, Paper 1 and Paper 2 of this doctoral research deliver a complete, integrated, regulatory-ready framework for continuous OSD manufacturing: one in which quality is designed in through QbD, continuously monitored through PAT, and continuously verified through RTRT. This is not the future of pharmaceutical manufacturing — it is its present, made rigorous by science, validated by data, and aligned with the highest standards of global pharmaceutical regulation. The patients who depend on consistently high-quality medicines deserve nothing less.

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