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Review Article

Advancing API Manufacturing: A Systematic Review of Process Analytical Technology Integrated with Artificial Intelligence and Quality by Digital Design

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Abstract

The pharmaceutical industry is moving toward Pharma 4.0, shifting from traditional batch manufacturing to connected, data-driven systems. Traditional quality checks done after production are slow and often result in material waste. To solve these problems, combining Process Analytical Technology (PAT) and Artificial Intelligence (AI) within a Quality by Digital Design (QbDD) framework offers a major step forward in drug manufacturing. This Systematic Literature Review examines this combination in Active Pharmaceutical Ingredient (API) manufacturing. Following PRISMA 2020 guidelines, a thorough search of ScienceDirect and Taylor & Francis databases found 14 peer-reviewed articles published between 2023 and 2026. The results show that advanced AI models, especially Convolutional Neural Networks (CNN) and YOLOv5, perform much better than traditional statistical methods when handling large and complex data from PAT sensors. These AI models support Real-Time Release Testing (RTRT) by accurately predicting multiple product quality measures at the same time. In addition, QbDD supports eco-friendly "Green-by-Design" approaches by using computer-assisted tools to improve the steps used to make drug compounds. Furthermore, Large Language Models (LLMs) offer Explainable AI (XAI) to turn complex computer predictions into clear, useful insights. Overall, this combination opens the path toward fully automated API manufacturing, though challenges related to computing power and regulatory approval still need to be resolved.

Keywords: process analytical technology; artificial intelligence; quality by digital design; API; pharmaceutical industry

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1 Introduction

The pharmaceutical industry is currently undergoing a significant paradigm shift, transitioning from traditional batch manufacturing toward Pharma 4.0—a digital transformation characterized by interconnectedness, real-time data, and autonomous decision-making [1]. In the context of Active Pharmaceutical Ingredient (API) manufacturing, maintaining consistent quality while ensuring high production efficiency remains a formidable challenge. Traditionally, quality assurance has relied on post-production laboratory testing, a time-consuming and often destructive process that inevitably leads to significant material waste and batch rejection if deviations occur [2].

To address these limitations, the International Council for Harmonisation (ICH) guidelines have advocated for the implementation of Quality by Digital Design (QbDD). Central to the successful execution of QbD is Process Analytical Technology (PAT). Recent advancements in PAT, such as the use of in-line process endoscopes and shadowgraph imaging, have enabled the real-time monitoring of particle dynamics and morphology during critical stages like continuous milling and dissolution [3], [4]. These tools allow for the immediate detection of process deviations, such as unwanted agglomeration, which could otherwise compromise the final product's efficacy.

However, the massive influx of high-dimensional data generated by PAT sensors presents a new challenge: data complexity. Conventional statistical methods often struggle to capture the non-linear and dynamic interactions inherent in complex manufacturing processes, such as high-shear wet granulation or electrospinning [5], [6]. This is where Artificial Intelligence (AI) and Machine Learning (ML) emerge as transformative catalysts. Modern AI architectures, including Convolutional Neural Networks (CNN) and YOLOv5, have demonstrated superior capabilities in component-based particle size measurement and the characterization of amorphous solid dispersions [6], [7].

The integration of AI within a Quality by Digital Design (QbDD) framework represents the next evolution of pharmaceutical manufacturing, facilitating a more sustainable and "Green-by-Design" approach [8], [9]. This synergy not only enhances the predictive accuracy of surrogate dissolution models but also enables Real-Time Release Testing (RTRT), ensuring that quality is guaranteed at every step of the process [3]. Furthermore, the emergence of Large Language Models (LLMs) offers new possibilities for generating original research hypotheses and providing explainable insights into complex batch interactions [10], [11].

Despite these advancements, a comprehensive synthesis specifically focusing on the integration of PAT, AI, and QbD in API manufacturing remains scarce. This Systematic Literature Review (SLR) aims to bridge this gap by analyzing 14 high-quality articles published between 2023 and 2026. By synthesizing these findings, this study provides a strategic roadmap for researchers and industrial pharmacists to transition toward a fully digitized and autonomous manufacturing landscape.

2 Method

The methodology of this systematic review was designed to identify, evaluate, and synthesize existing literature regarding the integration of Process Analytical Technology (PAT) and Artificial Intelligence (AI) in Active Pharmaceutical Ingredient (API) manufacturing. The study adheres to the PRISMA 2020 statement to ensure a rigorous and standardized reporting process.

2.1 Search Strategy and Data Source

A comprehensive literature search was conducted across two primary electronic databases ScienceDirect and Taylor & Francis. These databases were selected due to their extensive coverage of pharmaceutical sciences, chemical engineering, and advanced manufacturing technologies. The search utilized a combination of Boolean operators and specific keywords: "Process Analytical Technology" AND ("Pharmaceutical Industry" OR "Drug Manufacturing") AND "API". The search was restricted to peer-reviewed journal articles published in English to maintain the quality of the evidence.

Studies were evaluated on the following inclusion and exclusion criteria:

Inclusion Criteria

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1) Research focused on Active Pharmaceutical Ingredients (API) manufacturing or solid dosage form production.
2) Application of Process Analytical Technology (PAT) tools, such as NIR, Raman, Terahertz spectroscopy, or machine vision.
3) Integration of Artificial Intelligence (AI) or Machine Learning (ML) for data processing, predictive modeling, or quality control.
4) Articles published between 2023-2026.
5) Full-text articles available in English.

Exclusion Criteria

1) Review papers, book chapters, conference abstracts, and editorials.
2) Studies focused on clinical AI applications without a manufacturing context.
3) Research relying solely on conventional statistical methods (without advanced AI or machine learning components.

2.2 Selection Process

The study selection adhered to the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The systematic workflow from initially locating records to ultimately including 14 articles, illustrated in PRISMA 2020 flow diagram (Figure 1).

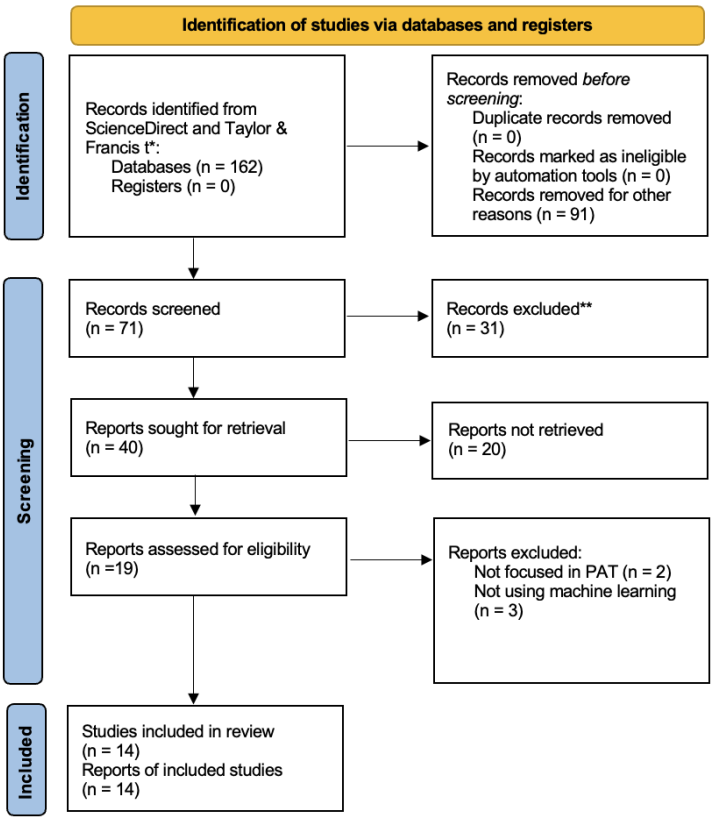

Figure 1. PRISMA flow diagram illustrating the systematic identification, screening, and selection process of the literature included in the review

3 Result and Discussion

3.1 Result

Articles published between 2023 and 2026 were included in this review. This time frame was selected to capture the most recent developments in the integration of Process Analytical Technology (PAT), Artificial Intelligence (AI), and Quality by Design (QbD) in API manufacturing and solid dosage form production, particularly following the rapid advancement of AI- and ML-based analytical approaches

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in pharmaceutical manufacturing. The general characteristics, technological focus, and thematic categorization of these studies are summarized in Table 1.

Table 1 Summary of Selected Literatures on PAT-AI Integration

Author (Year)	Core Technology	Process	AI & Digital Tools	Key Findings & Contributions
Bounab et al. (2025) [11]	AI	Direct Tablet Compression (DTC)	Multi-task Neural Networks & Gen-AI	Predicted tablet friability and hardness; utilized LLMs for causal analysis of batch acceptance.
Madarász et al. (2023)[3]	PAT & AI	Continuous Milling / In-line Endoscope	YOLOv5 (Object Detection)	Achieved real-time particle size measurement (200–1000 µm) for NaCl as a model API.
Taseva et al. (2023) [4]	AI	Flow-through Dissolution	Image Analysis & Classification	Automated characterization of drug dissolution and precipitation events in real-time.
Taseva et al. (2024) [12]	PAT	USP 4 Flow-through / Shadowgraph Imaging	Agglomeration Identification Method (AIM)	Developed an automated AI method for real-time detection of ibuprofen agglomerates.
Fazekas et al. (2025) [2]	PAT	UV Fluorescent Imaging	Machine Vision & AI	Developed a non-destructive system for measuring API concentration in tablets with high precision.
Teixeira & Benyahia (2025) [9]	QbDD	API Synthesis / Flow Chemistry	Computer-Aided Retrosynthesis (CAR)	Optimized shared synthetic routes for 11 APIs using "Green-by-Design" principles.
Munu et al. (2024) [13]	PAT & AI	High Shear Wet Granulation (HSWG)	Evolutionary Equation Discovery	Predicted granule and tablet properties by discovering mathematical laws from force-probe data.
Fazekas et al. (2024) [6]	PAT	Electrospinning / UV-Vis & Raman	Convolutional Neural Networks (CNN)	Monitored fiber diameter and drug concentration in amorphous solid dispersions (ASD).
Mustoe et al. (2025) [8]	QbDD	Sustainable Manufacturing / QbDD	Digital Twins & ML	Framework for accelerating drug development by replacing physical experiments with digital simulations.
Kálnai et al. (2025) [7]	PAT	Continuous Powder Feeding	YOLOv5 & Machine Vision	Simultaneous determination of component-based particle size and dissolution prediction.
Mészáros et al. (2024) [14]	PAT & AI	Continuous Blending / NIR	Dissolution Surrogate Model	Demonstrated Real-Time Release Testing (RRT) for blend uniformity and dissolution.
Benczúr et al. (2025) [15]	AI & QbDD	Bulk Powder Blends / Endoscopy	YOLOv5 Instance Segmentation	Simultaneously measured API concentration and particle size distribution in multi-component blends.
Anuschek et al. (2025) [16]	AI	Tablet Compression / Terahertz	THz-TDS Reflection Setup	Real-time monitoring of tablet porosity, thickness, and mass to ensure data integrity.
Munu et al. (2025) [5]	PAT & AI	Compaction Simulation (Styl'One)	Statistical & Machine Learning	Correlated in-line drag force measurements with the physical attributes of the final tablet.

*AI: Artificial Intelligence; PAT: Process Analytical Technology; QbDD: Quality by Digital Design; ML: Machine Learning; RTRT: Real-Time Release Testing; Opt: Optimization; Mon: Monitoring; QA: Quality Assurance.

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The results indicate that while spectroscopic tools like NIR and Raman remain fundamental for chemical identification, there is an increasing reliance on high-resolution imaging technologies. In-line process endoscopes and Shadowgraph Imaging (SGI) have emerged as powerful tools for real-time particle characterization in continuous milling and dissolution testing [3], [12]. Furthermore, the application of digital camera-based UV illumination has demonstrated high specificity and precision in monitoring low-dose API concentrations, providing a non-destructive alternative to HPLC [6].

Beyond the 14 core studies identified through the PRISMA search, several additional peer-reviewed articles were reviewed to further enrich the discussion of PAT-AI integration in API manufacturing. Foundational PAT-driven scale-up work by Jain et al. combined a Monte Carlo-based population balance solver with computational fluid dynamics (CFD) to predict needle-shaped API crystal size distribution across a 200-fold scale-up of crystallization, filtration, drying, and milling operations, achieving less than 10% deviation from measured D90 values [17]. In a related vein, Agrawal et al. demonstrated that coupling automated wet milling with in-situ particle video microscopy and dynamic image analysis accelerates data-rich particle engineering at the Drug Substance/Drug Product interface, using Lovastatin as a model compound [18]. These works illustrate that the value of PAT-AI convergence extends beyond post-hoc quality prediction to also enabling equipment-level automation and scale-up confidence.

Complementary evidence on the breadth of PAT platforms is provided by three additional works. Neugebauer et al. presented a comprehensive review of PAT methodologies specifically applied to solid API downstream processing, consolidating spectroscopic, imaging, and emerging in-line monitoring techniques at the drug-substance stage [19]. At a more granular equipment level, Feng Báez et al. evaluated a compact composite ultraviolet/near-infrared sensor array for concentration monitoring of solutions and suspensions, reporting chemometric accuracy comparable to established Raman spectrometers while addressing space constraints in miniaturized manufacturing platforms [20]. Complementing these sensing advances, Celikovic et al. demonstrated a control-oriented workflow that integrates an in-line PAT probe with a local-linear-model-tree algorithm to build both a model predictive controller and a granule-size soft sensor for twin-screw wet granulation, validated on a production-scale ConsiGmaTM-25 line [21].

3.2. Discussion

3.2.1 The Superiority of AI Architectures in Predictive Quality Control

The inherent superiority of advanced Artificial Intelligence (AI) architectures over traditional multivariate statistical methods lies in their capacity to process high-dimensional, non-linear data from PAT sensors without the need for simplified assumptions. Conventional chemometric tools, while useful for linear systems, often struggle with the complexity of real-time imaging and spectroscopic data, particularly when dealing with overlapping particles or fluctuating process conditions in dense powder environments. In contrast, deep learning frameworks such as Convolutional Neural Networks (CNN) and YOLOv5 have demonstrated remarkable robustness in segmenting and characterizing particle size distributions in-line, directly interpreting raw data from process endoscopes and shadowgraph imaging with significantly lower error rates than traditional thresholding techniques [3], [7]. This capability allows for a more granular and accurate understanding of process dynamics, facilitating the detection of subtle deviations that would otherwise be obscured in traditional data processing workflows.

AI-driven predictive modeling has redefined the boundaries of Real-Time Release Testing (RTRT) by providing high-fidelity surrogate models for complex quality attributes. Recent evidence in continuous tablet manufacturing shows that multi-task neural networks can concurrently predict multiple Critical Quality Attributes (CQAs), such as friability, hardness, and dissolution profiles, with a precision that significantly surpasses standard linear regressions [11], [14]. The emergence of Explainable AI (XAI) and generative frameworks further enhances this superiority by bridging the gap between predictive accuracy and regulatory transparency. By offering causal insights into batch acceptance and the underlying mechanisms of process interactions, these advanced architectures allow manufacturers to transition from

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simple binary "pass/fail" outcomes to a comprehensive, data-driven mastery of product quality and process control [11].

Complementing the CNN- and YOLOv5-driven approaches highlighted above, simpler artificial neural network (ANN) architectures have also proven effective for PAT-based quality prediction, indicating that AI superiority is not confined to deep learning alone. Ficzere et al. combined rapid (50 ms) UV imaging with ANN regression to achieve non-destructive, at-line content determination of colourless APIs, reporting relative prediction errors below 4.5% for amlodipine- and valsartan-containing tablets [22]. Similarly, chemometric models built on NIR and Raman spectroscopy have been extended beyond conventional detection ranges: Galata et al. showed that an in-line surrogate signal from an excipient (polyvinylpyrrolidone) could indirectly predict ultralow-dose (40–100 ppm) API concentrations during twin-screw wet granulation, with root-mean-square errors below 7.1 ppm [23]. Beyond conventional spectroscopic and imaging tools, alternative PAT modalities have also demonstrated batch-level monitoring capability; direct analysis in real-time mass spectrometry (DART-MS), combined with multi-way partial least squares modelling, enabled real-time fault detection and product-quality assessment during a botanical drug percolation process [24]. Collectively, these findings reinforce that AI-augmented PAT delivers predictive advantages across a broad spectrum of analytical and modelling techniques, not solely within image-based deep learning frameworks.

The value of AI-augmented PAT is further reinforced by three additional studies. Pathak et al. trained a convolutional neural network on more than 25,000 tablet images to automatically detect coating defects such as chipping, breaking, and colour non-uniformity, achieving high classification accuracy without manual feature engineering and illustrating the applicability of CNN-based vision beyond particle-size measurement [25]. In parallel, Gudena et al. developed a semi-mechanistic, hybrid model-based soft sensor to forecast particle size distribution in real time during the wet bead milling of concentrated nanosuspension-based long-acting injectable products, validating its prediction fidelity against production-scale batches [26]. Most directly relevant to RTRT, Honti et al. conducted a systematic comparison of mechanistic, data-driven, and hybrid surrogate models for the in vitro dissolution of tablets, introducing a novel serial hybrid architecture that couples an artificial neural network with a population balance model; their findings reinforce that hybrid approaches can combine the predictive flexibility of AI with the interpretability required for regulatory acceptance [27].

3.2.2 Quality by Digital Design (QbDD) and Sustainability

The transition from Quality by Design (QbD) to Quality by Digital Design (QbDD) represents a critical paradigm shift toward a more agile and data-driven pharmaceutical lifecycle [1], [8]. While QbD focuses on defining a design space through empirical experimentation, QbDD leverages digital twins, advanced data analytics, and AI to create a dynamic, predictive environment for drug development [1]. This digital-first approach significantly accelerates development timelines by replacing extensive physical "trial-and-error" experiments with in-silico simulations. For instance, the use of evolutionary equation discovery from in-line measurements in high-shear wet granulation (HSWG) provides a deep mechanistic understanding of process transmissions, enabling the prediction of tablet properties without exhaustive experimental iterations[5], [13]. Furthermore, the integration of generative AI and Large Language Models (LLMs) in automating research hypotheses and scientific documentation further streamlines the QbDD workflow, enhancing the overall efficiency of the development process (Elbadawi et al., 2024).
Beyond operational efficiency, the implementation of AI within the QbDD framework serves as a primary catalyst for "Green-by-Design" pharmaceuticals and long-term environmental sustainability [8], [9]. The synergy between Computer-Aided Retrosynthesis (CAR) and continuous flow chemistry enables the optimization of shared synthetic routes for multiple APIs, achieving high yields of up to 95% while drastically reducing solvent consumption and waste generation [9]. By predicting the environmental footprint of various manufacturing scenarios in-silico, QbDD facilitates the selection of the most sustainable reaction recipes before physical resources are consumed [8], [9]. This digital evolution not only ensures the robust quality of APIs but also addresses the industry's urgent need for resource efficiency

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and reduced carbon footprints, aligning modern pharmaceutical manufacturing with global sustainability goals [1].

Sustainability gains from PAT integration are not limited to synthetic route optimization; they also extend to ancillary manufacturing operations such as equipment cleaning and changeover. Aramouni et al. demonstrated that combining in-line PAT with optical imaging analysis during Clean-in-Place (CIP) validation enabled the identification of the governing cleaning mechanisms—dissolution versus mechanical shear—and, consequently, the most efficient and repeatable cleaning conditions for pharmaceutical equipment, significantly reducing solvent consumption [28]. This finding extends the "Green-by-Design" principle beyond API synthesis and formulation toward the broader manufacturing lifecycle.

Digital modelling approaches extend this sustainability-oriented, predictive paradigm beyond individual unit operations. Maharjan et al., in a broad review of digital twins across the pharmaceutical and biopharmaceutical development lifecycle, highlighted that PAT-integrated continuous manufacturing digital twins can substantially improve API consistency while supporting real-time monitoring, predictive analytics, and adaptive control, positioning digital twins as a natural extension of the QbDD framework toward fully autonomous, self-correcting manufacturing [29].

3.2.3 The Emergence of Generative AI and Explainability

A pivotal advancement identified in recent literature is the integration of Generative Artificial Intelligence and Large Language Models (LLMs) into pharmaceutical manufacturing workflows. Historically, the application of AI in Process Analytical Technology (PAT) was strictly confined to predictive tasks, such as regression for dissolution profiles or classification for particle detection. However, the paradigm is rapidly shifting toward models capable of complex cognitive tasks and causal reasoning. For instance, recent studies have demonstrated the unprecedented capability of advanced LLMs, such as GPT-4, to autonomously synthesize vast amounts of multidisciplinary data to generate original research hypotheses and propose novel formulation designs [10]. In a manufacturing context, multi-task AI frameworks are now leveraging generative text models to interpret complex tabular data from direct tablet compression processes, moving beyond mere numerical prediction to active process evaluation [11].

The generative capability provides a robust solution to one of the most significant barriers to AI adoption in the highly regulated pharmaceutical sector: the "black-box" nature of deep learning algorithms. For regulatory compliance and effective Quality by Design (QbD) implementation, providing a simple binary outcome—such as batch acceptance or rejection—is fundamentally insufficient; manufacturers and regulatory bodies require a transparent understanding of the root causes behind a process deviation [1]. By incorporating Explainable AI (XAI) principles, novel frameworks utilize LLMs to translate intricate multivariate sensor data into human-readable textual insights, offering explicit, mechanistic justifications for quality predictions [11]. This integration of generative explainability not only fosters greater trust among regulatory agencies but also completes the critical feedback loop required to realize fully autonomous, self-correcting manufacturing systems.

3.2.4 Technical Challenges and Regulatory Considerations

Despite the transformative potential of AI-integrated PAT systems, several technical bottlenecks continue to impede their widespread industrial adoption. Foremost among these is the immense computational demand required for continuous, real-time data processing. In-line monitoring using high-resolution instruments, such as process endoscopes or shadowgraph imaging, generates massive volumes of complex visual data. Processing this data instantaneously via deep learning algorithms (e.g., CNNs or YOLOv5) to enable active process control necessitates significant investments in high-performance computing infrastructure and edge-computing capabilities on the factory floor [3], [12], [14]. Maintaining model robustness over time remains a persistent challenge. AI surrogate models and imaging classifiers are highly sensitive to matrix interference; minor lot-to-lot variations in raw materials or excipient properties can alter background spectral signatures or visual contrasts, thereby necessitating frequent re-calibration and continuous model updating to prevent drifts in predictive accuracy [6].

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Beyond hardware and algorithmic constraints, the transition to QbDD presents unprecedented regulatory hurdles. Global health authorities, including the FDA and EMA, mandate rigorous validation protocols to ensure unwavering patient safety and product efficacy. The inherently opaque, "black-box" nature of advanced neural networks complicates traditional validation procedures, as tracing the exact mechanistic rationale behind an AI-generated release decision is often difficult. The current lack of standardized, global regulatory guidelines for continuously learning and self-correcting manufacturing systems creates a barrier to rapid commercialization. To navigate this landscape, the pharmaceutical industry must actively collaborate with regulatory bodies to establish clear compliance pathways, prioritizing the integration of Explainable AI (XAI) frameworks that can provide transparent, verifiable justifications for process interventions [1], [11].

Adoption barriers are not confined to computational and regulatory constraints alone. A review by Liu et al. on PAT- and algorithm-integrated pharmaceutical continuous manufacturing highlighted that, despite rapid global progress, regional disparities persist; in China, for example, the advancement of automated continuous manufacturing has been comparatively slower due to limited technical knowledge of the relevant technologies and a shortage of qualified personnel [30]. This observation suggests that, alongside computing infrastructure and regulatory harmonization, workforce training and knowledge transfer represent an additional, often overlooked, barrier to the global scaling of PAT-AI-QbDD integration.

4 Conclusion

The integration of PAT and AI within the QbDD framework marks a pivotal evolution in API manufacturing, transitioning the industry from reactive quality control to predictive, autonomous operations. This systematic review demonstrates that advanced deep learning architectures, particularly CNN and YOLOv5, significantly outperform traditional multivariate statistics in processing complex, high-dimensional sensor data. By enabling highly accurate, real-time particle characterization and dissolution prediction, these AI-driven surrogate models successfully facilitate RTRT. This advancement effectively minimizes material waste and bypasses the need for time-consuming, destructive end-product testing, ensuring that CQAs are consistently met throughout the production lifecycle.

Beyond operational efficiency, the synergy of AI and PAT serves as a critical enabler for sustainable, "Green-by-Design" pharmaceutical manufacturing. Innovations such as CAR combined with continuous flow chemistry allow for the optimization of synthetic routes, drastically reducing environmental footprints. Furthermore, the emerging integration of LLMs provides the necessary XAI to demystify "black-box" algorithmic predictions, translating complex data into actionable, regulatory-compliant insights. However, to achieve full-scale industrial commercialization, future research must address ongoing challenges related to model robustness against matrix variability and the high computational demands of continuous image processing. Ultimately, proactive collaboration between the pharmaceutical industry and global regulatory agencies is essential to establish standardized compliance guidelines.

5 Bibliography

[1] R. Abdulhussain *et al.*, "The integration of artificial intelligence through quality by digital design for sustainable pharmaceutical manufacturing," *Int. J. Pharm.*, vol. 693, hlm. 126682, 2026, doi: https://doi.org/10.1016/j.ijpharm.2026.126682.

[2] B. Fazekas, D. G. Pogány, D. L. Galata, Z. K. Nagy, L. A. Mészáros, dan E. Hirsch, "Characterization of digital camera-based UV illumination fluorescent imaging for concentration measurement with limit of detection, specificity and precision," *Eur. J. Pharm. Sci.*, vol. 210, hlm. 107117, 2025, doi: https://doi.org/10.1016/j.ejps.2025.107117.

[3] L. Madarász, L. A. Mészáros, Á. Köte, A. Farkas, dan Z. K. Nagy, "AI-based analysis of in-line process endoscope images for real-time particle size measurement in a continuous pharmaceutical

milling process," *Int. J. Pharm.*, vol. 641, hlm. 123060, Jun 2023, doi: 10.1016/j.ijpharm.2023.123060.

[4] A. R. Taseva, T. Persoons, dan D. M. D'Arcy, "Application of an AI image analysis and classification approach to characterise dissolution and precipitation events in the flow through apparatus," *Eur. J. Pharm. Biopharm.*, vol. 189, hlm. 36–47, 2023, doi: https://doi.org/10.1016/j.ejpb.2023.04.020.

[5] I. Munu, A. L. Nicusan, J. Crooks, K. Pitt, C. Windows-Yule, dan A. Ingram, "Using in-line measurement and statistical analyses to predict tablet properties compressed using a Styl'One compaction simulator: A high shear wet granulation study," *Int. J. Pharm.*, vol. 669, hlm. 125098, 2025, doi: https://doi.org/10.1016/j.ijpharm.2024.125098.

[6] B. Fazekas, O. Péterfi, D. L. Galata, Z. K. Nagy, dan E. Hirsch, "Process analytical technology based quality assurance of API concentration and fiber diameter of electrospun amorphous solid dispersions," *Eur. J. Pharm. Biopharm.*, vol. 204, hlm. 114529, 2024, doi: https://doi.org/10.1016/j.ejpb.2024.114529.

[7] Á. Kálnai *et al.*, "Real-time component-based particle size measurement and dissolution prediction during continuous powder feeding using machine vision and artificial intelligence-based object detection," *Eur. J. Pharm. Sci.*, vol. 209, hlm. 107080, Jun 2025, doi: 10.1016/j.ejps.2025.107080.

[8] C. L. Mustoe *et al.*, "Quality by digital design to accelerate sustainable medicines development," *Int. J. Pharm.*, vol. 681, hlm. 125625, Agu 2025, doi: 10.1016/j.ijpharm.2025.125625.

[9] R. I. Teixeira dan B. Benyahia, "Design and optimization of a shared synthetic route for multiple active pharmaceutical ingredients through combined computer aided retrosynthesis and flow chemistry," *Chem. Eng. Res. Des.*, vol. 216, hlm. 367–375, Apr 2025, doi: 10.1016/j.cherd.2025.03.004.

[10] M. Elbadawi, H. Li, A. W. Basit, dan S. Gaisford, "The role of artificial intelligence in generating original scientific research," *Int. J. Pharm.*, vol. 652, hlm. 123741, Mar 2024, doi: 10.1016/j.ijpharm.2023.123741.

[11] Y. Bounab, O. Antikainen, M. Sivén, dan A. Juppo, "Advancing Direct Tablet Compression with AI: A multi-task framework for quality control, batch acceptance, and causal analysis," *Eur. J. Pharm. Sci.*, vol. 212, hlm. 107142, Sep 2025, doi: 10.1016/j.ejps.2025.107142.

[12] A. R. Taseva, T. Persoons, A. M. Healy, dan D. M. D'Arcy, "Application of shadowgraph imaging (SGI) particle characterisation data to interpret the impact of varying test conditions on powder dissolution and to develop an automated agglomeration identification method (AIM) in the USP flow-through apparatus," *Int. J. Pharm.*, vol. 666, hlm. 124778, Des 2024, doi: 10.1016/j.ijpharm.2024.124778.

[13] I. Munu, A. L. Nicusan, J. Crooks, K. Pitt, C. Windows-Yule, dan A. Ingram, "Predicting tablet properties using In-Line measurements and evolutionary equation Discovery: A high shear wet granulation study," *Int. J. Pharm.*, vol. 661, hlm. 124405, Agu 2024, doi: 10.1016/j.ijpharm.2024.124405.

[14] L. A. Mészáros, L. Madarász, S. Kádár, M. Ficzere, A. Farkas, dan Z. K. Nagy, "Machine vision-based non-destructive dissolution prediction of meloxicam-containing tablets," *Int. J. Pharm.*, vol. 655, hlm. 124013, 2024, doi: https://doi.org/10.1016/j.ijpharm.2024.124013.

[15] M. Benczúr, M. Ficzere, O. Péterfi, Á. Kálnai, Z. K. Nagy, dan D. L. Galata, "Simultaneous in-line particle size distribution determination of drug and excipient from their powder blend using endoscopic imaging and AI," *Eur. J. Pharm. Sci.*, vol. 215, hlm. 107339, Des 2025, doi: 10.1016/j.ejps.2025.107339.

[16] M. Anuschek, T. K. Vilhelmsen, J. A. Zeitler, dan J. Rantanen, "In-line monitoring of tablet compression with terahertz time-domain spectroscopy for physical tablet characteristics," *Int. J. Pharm.*, vol. 685, hlm. 126273, 2025, doi: https://doi.org/10.1016/j.ijpharm.2025.126273.

[17] D. Jain, V. Dalvi, C. Mathpati, dan J. Kant, "Process Analytical Technology as an enabling tool for scale up of crystallization, filtration, drying and milling," *Chem. Eng. Res. Des.*, vol. 190, hlm. 117–128, Feb 2023, doi: 10.1016/j.cherd.2022.11.045.

[18] S. Agrawal, S. H. Rawal, V. R. Reddy, dan J. M. Merritt, "Use of automation, dynamic image analysis, and process analytical technologies to enable data rich particle engineering efforts at the Drug Substance / Drug Product interface: A case study using Lovastatin," *Chem. Eng. Res. Des.*, vol. 205, hlm. 578–590, Mei 2024, doi: 10.1016/j.cherd.2024.04.032.

[19] P. Neugebauer, M. Zettl, D. Moser, J. Poms, L. Kuchler, dan S. Sacher, "Process analytical technology in Downstream-Processing of Drug Substances– A review," *Int. J. Pharm.*, vol. 661, hlm. 124412, Agu 2024, doi: 10.1016/j.ijpharm.2024.124412.

[20] J. P. Feng Báez, M. V. George De la Rosa, B. B. Alvarado-Hernández, R. J. Romañach, dan T. Stelzer, "Evaluation of a compact composite sensor array for concentration monitoring of solutions and suspensions via multivariate analysis," *J. Pharm. Biomed. Anal.*, vol. 233, hlm. 115451, Sep 2023, doi: 10.1016/j.jpba.2023.115451.

[21] S. Celikovic, J. Poms, J. Khinast, M. Horn, dan J. Rehrl, "Control oriented modeling of twin-screw granulation in the ConsiGmaTM-25 production plant," *Int. J. Pharm.*, vol. 641, hlm. 123038, 2023, doi: https://doi.org/10.1016/j.ijpharm.2023.123038.

[22] M. Ficzere *et al.*, "UV imaging for the rapid at-line content determination of different colourless APIs in their tablets with artificial neural networks," *Int. J. Pharm.*, vol. 657, hlm. 124174, 2024, doi: https://doi.org/10.1016/j.ijpharm.2024.124174.

[23] D. L. Galata *et al.*, "In-line indirect concentration measurement of ultralow dose API during twin-screw wet granulation based on NIR and Raman spectroscopy," *Int. J. Pharm.*, vol. 664, hlm. 124650, 2024, doi: https://doi.org/10.1016/j.ijpharm.2024.124650.

[24] L. Wang, S. Zeng, T. Chen, dan H. Qu, "Direct analysis in real time mass spectrometry, a process analytical technology tool for real-time process monitoring in botanical drug manufacturing," *J. Pharm. Biomed. Anal.*, vol. 91, hlm. 202–209, Mar 2014, doi: 10.1016/j.jpba.2013.12.034.

[25] K. A. Pathak, P. Kafle, dan A. Vikram, "Deep learning-based defect detection in film-coated tablets using a convolutional neural network," *Int. J. Pharm.*, vol. 671, hlm. 125220, Feb 2025, doi: 10.1016/j.ijpharm.2025.125220.

[26] K. Gudena *et al.*, "Development of a model-based soft-sensor for real time forecasting of particle size distribution during wet bead milling of concentrated nanosuspension-based long acting injectable (LAI) drug product," *Int. J. Pharm.*, vol. 683, hlm. 126064, Okt 2025, doi: 10.1016/j.ijpharm.2025.126064.

[27] B. Honti, G. Mihályi, Z. K. Nagy, E. Borbás, H. Pataki, dan B. Nagy, "Mechanistic, data-driven, and hybrid models: A critical comparison in surrogate drug dissolution modeling," *Int. J. Pharm.*, vol. 688, hlm. 126474, Jan 2026, doi: 10.1016/j.ijpharm.2025.126474.

[28] N. A. K. Aramouni, M. Steiner-Browne, dan R. Mouras, "Application of process analytical technology (PAT) in real-time monitoring of pharmaceutical cleaning process: Unveiling the cleaning mechanisms governing the cleaning-in-place (CIP)," *Process Saf. Environ. Prot.*, vol. 177, hlm. 212–222, 2023, doi: https://doi.org/10.1016/j.psep.2023.07.010.

[29] R. Maharjan, N. A. Kim, K. H. Kim, dan S. H. Jeong, "Transformative roles of digital twins from drug discovery to continuous manufacturing: pharmaceutical and biopharmaceutical perspectives," *Int. J. Pharm. X*, vol. 10, hlm. 100409, Des 2025, doi: 10.1016/j.ijpx.2025.100409.

[30] P. Liu *et al.*, "Process analytical technologies and self-optimization algorithms in automated pharmaceutical continuous manufacturing," *Chin. Chem. Lett.*, vol. 35, no. 3, hlm. 108877, Mar 2024, doi: 10.1016/j.cclet.2023.108877.