Innovations in Pharmaceutical Formulation Development: Harnessing Process Analytical Technology (PAT) for Future Healthcare

Uday Kumar Thummala

Professor,

Department of Pharmaceutics

Aditya College of Pharmacy

Surampalem, India

udaykumar.chowdary16@gmail.com

Divya Narla

Associate Professor,

Department of Pharmaceutical Analysis

Aditya College of Pharmacy

Surampalem, India

divyanarla@gmail.com

ABSTRACT

The landscape of pharmacy and nursing is rapidly evolving, driven by technological advancements that shape the formulation and administration of medicines. This chapter delves into the cutting-edge realm of Process Analytical Technology (PAT) and its pivotal role in shaping the future of pharmaceutical formulation development. PAT revolutionizes the way pharmaceutical products are designed, analyzed, and produced by enabling real-time monitoring, control, and optimization of manufacturing processes. This chapter explores recent advances in PAT, including spectroscopic techniques, sensor technologies, data analytics, and quality-by-design (QbD) approaches.

Keywords— Process Analytical Technology; Pharmaceutical formulation; Real-time monitoring, Quality-by-design, Advanced analytics.

# INTRODUCTION

In the dynamic realm of healthcare, the fields of pharmacy and nursing have been in a state of constant evolution, responding to the pressing need for more effective and efficient approaches to medical treatment. A fundamental pillar of this evolution lies in the domain of pharmaceutical formulation development, where the art and science of crafting medications have undergone remarkable shifts over time. Traditional practices, while invaluable in their contributions, are now being interwoven with cutting-edge technological advancements that are shaping the trajectory of this pivotal discipline[1].

Historically, pharmaceutical formulation development primarily revolved around empirical experimentation, where trial and error guided the crafting of medicines. Formulation scientists relied on a blend of intuition, experience, and rudimentary analytical techniques to create pharmaceutical products. However, the constraints of this approach were evident, often resulting in suboptimal drug delivery, variable efficacy, and challenges in scalability.

The advent of modern pharmaceutical science brought forward methodologies that introduced greater precision and predictability into formulation development. The concept of Quality-by-Design (QbD) emerged, advocating for a systematic approach that considers the influence of formulation and process variables on the final product's performance. This shift heralded a more structured and holistic understanding of how formulations could be optimized to ensure consistent therapeutic outcomes.

In the contemporary landscape, the role of technological advancements in pharmaceutical formulation development cannot be overstated. A convergence of diverse technologies, ranging from advanced analytical instruments to computational modeling tools, has spurred transformative changes. The assimilation of these innovations has elevated pharmaceutical formulation from an empirical art to a data-driven science.

Technological breakthroughs have enabled the exploration of molecular structures with unprecedented precision, facilitating the design of drug molecules with optimal physicochemical properties. Analytical instruments, such as high-resolution mass spectrometers and nuclear magnetic resonance (NMR) spectrometers, have empowered researchers to unravel the intricate details of drug-substance interactions and degradation pathways.

Moreover, the integration of computational methods, including molecular modeling and virtual screening, expedites the identification of potential drug candidates and predicts their behavior in various formulations. This computational prowess, coupled with high-throughput screening techniques, accelerates the drug discovery process, allowing for the assessment of thousands of compounds in significantly shorter timeframes[2].

The introduction of process analytical technology (PAT) has been a game-changer in the manufacturing phase. PAT leverages real-time monitoring, data analysis, and feedback control to ensure consistent product quality during production. This approach not only reduces batch-to-batch variability but also minimizes the risk of producing out-of-specification products [3].

In the subsequent sections of this chapter, we will delve deeper into one of the most transformative technological trends within pharmaceutical formulation development: Process Analytical Technology (PAT). This technology has not only ushered in an era of real-time monitoring and optimization but also holds the potential to reshape the future of pharmaceutical manufacturing.

# UNDERSTANDING PROCESS ANALYTICAL TECHNOLOGY (PAT)

The advent of Process Analytical Technology (PAT) has heralded a new era in pharmaceutical formulation development and manufacturing. PAT encompasses a comprehensive set of principles, tools, and strategies that empower pharmaceutical scientists and engineers to monitor, control, and optimize manufacturing processes in real time. By integrating advanced analytical techniques, data management, and automation, PAT shifts the focus from post-process quality testing to proactive quality assurance throughout the entire manufacturing lifecycle[4].

## **Definition and Principles of PAT**

At its core, PAT is founded on the principles of continuous improvement, risk management, and science-based decision-making. It is driven by the imperative to enhance product quality and process efficiency while minimizing variability and waste. PAT encourages a shift from traditional batch-based processes to continuous or semi-continuous manufacturing, where processes are dynamically adjusted to maintain product specifications [5].

Key principles of PAT include:

**Real-time Monitoring:** PAT employs a range of analytical technologies to monitor critical process parameters (CPPs) and critical quality attributes (CQAs) in real time. These measurements provide immediate insights into the state of the process, enabling rapid intervention if deviations occur.

**Multivariate Analysis:** PAT leverages multivariate analysis techniques to correlate complex data sets, identifying relationships between process variables and product attributes. This enables the identification of key factors influencing product quality and process performance.

**Process Control and Optimization:** By harnessing real-time data, PAT enables dynamic control and optimization of manufacturing processes. This leads to reduced variability, enhanced yield, and improved product consistency.

**Risk Assessment and Mitigation:** PAT integrates risk assessment methodologies to identify and mitigate potential risks to product quality. This proactive approach minimizes the likelihood of product failures and costly recalls.

## **PAT vs. Traditional Approaches: A Paradigm Shift**

The transition from traditional batch manufacturing to PAT-driven processes marks a paradigm shift in pharmaceutical formulation development and manufacturing. Traditional approaches involve periodic sampling and offline analysis of samples to ensure product quality. However, this approach has limitations:

**Time Lag:** Traditional methods provide retrospective insights, with data collected after the process has already occurred. This time lag can lead to the production of substandard batches before deviations are detected.

**Limited Data:** Traditional methods rely on a limited number of samples, which may not fully capture process variability. This increases the risk of producing batches that deviate from specifications.

**Resource Intensive:** Offline testing requires significant resources and time, often resulting in delays and increased production costs.

In contrast, PAT offers a transformative alternative:

**Real-time Insights:** PAT provides real-time data on process performance, allowing for immediate corrective actions if deviations occur. This prevents the production of non-conforming batches.

**Enhanced Understanding:** By continuously monitoring process variables and their impact on product quality, PAT enables a deeper understanding of the underlying relationships.

**Efficiency and Cost Savings:** PAT-driven processes are more efficient and cost-effective due to reduced material waste, shorter processing times, and fewer batch failures [6]. A comparison of Traditional versus Process analytical technology (PAT) is provided in Table 1.

**Table 1: Comparison of Traditional Approaches and PAT**

|  |  |  |
| --- | --- | --- |
| **Aspect** | **Traditional Approaches** | **Process Analytical Technology (PAT)** |
| Data Collection | Offline sampling and testing | Real-time monitoring and analysis |
| Decision-making | Reactive responses to deviations | Proactive adjustments for quality |
| Process Optimization | Limited data for optimization | Continuous optimization strategies |
| Resource Utilization | Suboptimal resource allocation | Improved efficiency and reduced waste |
| Regulatory Compliance | Conventional compliance assurance | Enhanced compliance with real-time data |
| Time-to-Market | Slower approval and market entry | Expedited approval with improved data |

# SPECTROSCOPIC TECHNIQUES FOR REAL-TIME ANALYSIS

Real-time analysis is at the heart of Process Analytical Technology (PAT), revolutionizing how pharmaceutical formulations are monitored and controlled during manufacturing. Spectroscopic techniques, with their ability to provide rapid and non-destructive insights into chemical composition, have emerged as cornerstones of PAT. This section explores some of the key spectroscopic techniques and their applications within the realm of pharmaceutical formulation development.

## **Near-Infrared Spectroscopy (NIRS)**

Near-Infrared Spectroscopy (NIRS) is a powerful technique that leverages the absorption of near-infrared light by molecular vibrations. NIRS is particularly adept at quantifying the chemical composition of complex mixtures, making it invaluable in pharmaceutical formulation analysis. By shining near-infrared light onto a sample and analyzing the reflected or transmitted light, NIRS can reveal information about the types and concentrations of chemical bonds present [7].

## **Raman Spectroscopy**

Raman Spectroscopy is based on the inelastic scattering of light, which provides insights into molecular vibrations and energy levels. This technique offers advantages such as high specificity and minimal sample preparation requirements. Raman spectroscopy is capable of identifying molecular structures, polymorphic forms, and even detecting trace impurities, making it indispensable for real-time analysis in pharmaceutical manufacturing [8].

## **Mid-Infrared Spectroscopy**

Mid-Infrared Spectroscopy involves the absorption of mid-infrared light by molecular bonds, resulting in characteristic vibrational spectra. This technique is particularly sensitive to functional groups within molecules, enabling the identification of chemical compounds and the quantification of specific components. Mid-infrared spectroscopy is versatile and applicable to a wide range of pharmaceutical products, including solid dosage forms, liquids, and even gases [9].

## **Advantages and Applications**

Spectroscopic techniques offer a multitude of advantages in the context of pharmaceutical formulation development [10], [11]:

**Non-Destructive Analysis:** Spectroscopic methods are non-destructive, allowing for real-time monitoring without altering the sample's integrity. This is crucial for maintaining the quality and consistency of pharmaceutical products.

**Rapid Measurements:** Spectroscopic techniques provide rapid results, enabling quick decision-making and real-time adjustments during manufacturing processes.

**Reduced Sample Size:** These techniques often require minimal sample preparation and smaller sample sizes compared to traditional analytical methods, minimizing material waste.

**Multivariate Analysis:** Spectroscopic data can be subjected to multivariate analysis techniques, allowing for the detection of subtle variations in complex formulations and correlations between variables.

The applications of spectroscopic techniques within pharmaceutical formulation development are wide-ranging:

**Blend Uniformity:** Spectroscopy can assess the uniformity of blends in solid dosage forms, ensuring consistent distribution of active ingredients.

**Endpoint Detection:** These techniques aid in determining the endpoint of processes such as drying, granulation, and coating.

**Polymorph Detection:** Spectroscopy assists in identifying polymorphic forms of drug substances, which can have significant implications for product stability and efficacy.

**Real-time Release Testing:** Spectroscopic methods enable real-time release testing, expediting the availability of pharmaceutical products while ensuring quality.

**Continuous Manufacturing:** Spectroscopic analysis is pivotal in continuous manufacturing setups, allowing for constant monitoring and control of product quality.

# SENSOR INNOVATIONS IN PAT

Process Analytical Technology (PAT) is driven by the integration of advanced sensors that provide real-time insights into manufacturing processes. These sensors play a pivotal role in monitoring critical parameters, enabling precise control, and ensuring the quality of pharmaceutical formulations. This section delves into the innovative sensor technologies that are shaping the landscape of pharmaceutical manufacturing within the framework of PAT [12]. The sensor technologies in PAT are listed out in Table 2.

**Table 2: Sensor Technologies in PAT**

|  |  |  |
| --- | --- | --- |
| **Sensor Technology** | **Working Principle** | **Applications in Pharmaceutical Manufacturing** |
| Wireless Sensors | IoT-enabled, remote data collection | Continuous monitoring in manufacturing |
| Electrochemical Sensors | Chemical reactions generate electrical signals | pH monitoring, dissolved oxygen detection |
| Microfluidic Devices | Manipulation of small liquid volumes | Real-time analysis of flow rates, viscosity |
| Infrared Spectroscopy | Absorption of infrared light by molecules | Identification of polymorphic forms, blends |

## **Wireless Sensors and IoT integration**

Wireless sensors and the Internet of Things (IoT) have revolutionized data acquisition and process monitoring. These sensors are embedded within equipment and manufacturing units, communicating real-time data to central systems. IoT integration facilitates seamless connectivity, enabling remote monitoring and control of processes. Wireless sensors are particularly advantageous in continuous manufacturing setups, offering flexibility, scalability, and the ability to gather data from diverse points within a manufacturing line [13].

## **Electrochemical Sensors**

Electrochemical sensors are highly sensitive and selective tools used for monitoring chemical reactions and analyte concentrations. These sensors work by converting chemical information into electrical signals, which can be translated into meaningful data. In pharmaceutical manufacturing, electrochemical sensors are employed to monitor parameters such as pH, dissolved oxygen, and conductivity. Their ability to provide real-time, in-line measurements contributes to the optimization of reactions and the assurance of product quality.

## **Microfluidic Devices**

Microfluidic devices offer a novel approach to process monitoring and analysis. These miniaturized systems manipulate tiny volumes of liquids within channels and chambers, allowing for rapid and precise analysis. Microfluidic sensors can assess properties such as viscosity, flow rate, and particle size distribution. Their compact size, reduced sample requirements, and high throughput capabilities make them ideal for continuous monitoring in pharmaceutical manufacturing [14].

## **Enhancing Data Collection and Analysis**

The integration of innovative sensor technologies within PAT enhances data collection and analysis in several ways:

**Real-time Monitoring:** Sensors provide immediate insights into process dynamics, allowing for timely adjustments and interventions to maintain product quality.

**High Precision:** Advanced sensors offer higher accuracy and sensitivity compared to traditional measurement methods, leading to improved data quality.

**Data Fusion:** Multiple sensors can be combined to provide a comprehensive view of the process, offering a holistic understanding of the interplay between variables.

**Automated Feedback:** Sensor data can trigger automated responses, such as adjustments to process parameters or the initiation of control actions.

**Predictive Analytics:** Sensor-generated data can be harnessed for predictive modeling, enabling the anticipation of deviations and proactive quality management [15].

# DATA ANALYTICS AND MACHINE LEARNING IN PAT

## **Data Analytics and Machine Learning in PAT**

In the era of Process Analytical Technology (PAT), data analytics and machine learning have emerged as transformative tools for extracting insights, optimizing processes, and enabling real-time decision-making within pharmaceutical manufacturing. This section delves into the role of data analytics and machine learning in enhancing the efficacy and efficiency of PAT-driven formulation development. The applications of Machine learning in PAT are listed out in Table 3.

**Table 3: Machine Learning Applications in PAT**

|  |  |  |
| --- | --- | --- |
| **Machine Learning Application** | **Purpose** | **Benefits** |
| Predictive Modeling | Forecasting process behavior based on data | Optimized processes, reduced variability |
| Anomaly Detection | Identifying deviations from normal patterns | Early detection of process irregularities |
| Process Optimization | Identifying optimal process conditions | Enhanced efficiency and resource usage |
| Quality Prediction | Estimating final product quality | Real-time assurance of product attributes |

## **Big Data in Pharmaceutical Manufacturing**

The proliferation of data in pharmaceutical manufacturing has given rise to the concept of "big data." This encompasses the vast amount of information generated from various sources, including sensors, instruments, and production processes. In PAT, big data is harnessed to identify patterns, correlations, and trends that might not be discernible through traditional analysis methods. By leveraging big data, manufacturers gain a comprehensive view of their processes, leading to better-informed decisions [16].

## **Predictive Modeling and Process Optimization**

Machine learning techniques enable the creation of predictive models that anticipate process behavior and outcomes based on historical and real-time data. These models can predict critical quality attributes (CQAs) and evaluate the impact of process parameters on product quality. By training on large datasets, machine learning algorithms refine their predictions over time, allowing for process optimization and the identification of optimal conditions that lead to desired product attributes [9].

## **Real-time Decision-making**

One of the most remarkable aspects of data analytics and machine learning in PAT is their capacity to facilitate real-time decision-making. By continuously analyzing data from sensors and other sources, these technologies empower operators and engineers to make instant adjustments to maintain process integrity and ensure product quality. Real-time decision-making reduces the risk of deviations and facilitates agile responses to unforeseen challenges [17].

Incorporating data analytics and machine learning in PAT offers several advantages[18]:

**Efficient Problem Detection:** Analytics identify anomalies and deviations early, enabling swift troubleshooting and corrective actions.

**Process Understanding:** Analyzing large datasets provides insights into complex relationships between variables, enhancing process understanding.

**Reduced Variability:** Predictive modeling and optimization minimize variability, leading to consistent product quality and reduced waste.

**Resource Optimization:** Machine learning identifies optimal process conditions, leading to enhanced resource utilization and cost savings.

**Regulatory Compliance:** Accurate predictive models can be integrated into Quality-by-Design (QbD) approaches, facilitating compliance with regulatory requirements.

# QUALITY-BY-DESIGN (QBD) AND PAT

The fusion of Quality-by-Design (QbD) principles with Process Analytical Technology (PAT) represents a potent synergy that drives the evolution of pharmaceutical formulation development and manufacturing. QbD is a systematic approach that emphasizes the design and control of processes to ensure desired product quality. When integrated with PAT, it fosters a comprehensive understanding of processes, facilitates risk assessment, and expedites regulatory compliance. This section delves into the symbiotic relationship between QbD and PAT, highlighting their combined impact on pharmaceutical manufacturing [19].

## **Integrating PAT into QbD Framework**

PAT complements the QbD framework by providing real-time data on critical process parameters (CPPs) and critical quality attributes (CQAs). This integration enhances process knowledge, enabling a more comprehensive control strategy. By incorporating PAT insights, QbD practitioners can optimize formulation design, identify potential sources of variability, and develop robust manufacturing processes that consistently yield high-quality products.

## **Risk Assessment and Mitigation**

The combined power of QbD and PAT extends to risk assessment and mitigation. QbD's proactive approach to risk management is fortified by the continuous data stream from PAT, allowing for early detection of deviations and potential failures. This real-time insight enables manufacturers to take corrective actions swiftly, minimizing the impact of risks and ensuring that products meet pre-defined quality standards.

## **Accelerating Regulatory Approval**

QbD and PAT collaboration accelerates regulatory approval processes. The comprehensive understanding of processes and the availability of real-time data instill confidence in regulatory agencies that products are consistently manufactured with high quality. This can lead to faster review and approval, reducing time-to-market for new pharmaceutical products. Moreover, the incorporation of QbD principles aligns with regulators' increasing focus on science-based approaches and risk-based assessments.

The benefits of QbD-PAT integration are manifold:

**Enhanced Process Understanding:** The combination of QbD and PAT offers a holistic understanding of processes, enabling precise control and optimization.

**Reduced Variability:** Continuous monitoring through PAT contributes to process stability, reducing batch-to-batch variability.

**Early Detection of Deviations:** PAT data allows for real-time identification of deviations, minimizing the likelihood of producing out-of-specification batches.

**Regulatory Confidence:** The integration of QbD and PAT demonstrates a commitment to quality, bolstering regulatory confidence in product consistency.

**Efficient Resource Allocation:** By identifying critical process parameters, QbD-PAT integration optimizes resource utilization and reduces waste[20]

# CHALLENGES AND FUTURE DIRECTIONS

While Process Analytical Technology (PAT) holds immense promise for transforming pharmaceutical formulation development, its implementation is not without challenges. This section explores the hurdles faced by the industry in adopting PAT and envisions the future directions that could shape the evolution of this innovative approach[21].

## **Regulatory and Compliance Challenges**

Integrating PAT into pharmaceutical manufacturing processes requires careful consideration of regulatory standards and compliance requirements. Regulatory agencies may require substantial evidence to demonstrate the equivalency of PAT-driven processes to traditional methods. Additionally, the dynamic nature of real-time monitoring raises questions about data integrity, security, and the validation of analytical methods. Striking a balance between innovation and regulatory compliance remains a pressing challenge[22].

## **Training and Skill Development**

Embracing PAT demands a skilled workforce capable of utilizing advanced technologies and analyzing complex data. Pharmaceutical professionals must be adept at operating analytical instruments, interpreting spectroscopic data, and harnessing machine learning techniques. Bridging the gap between traditional expertise and emerging technological fluency is essential for successful PAT implementation. Training programs that equip professionals with these skills will be pivotal in overcoming this challenge[23].

## **Future Prospects of PAT in Healthcare**

The future of Process Analytical Technology is poised to be transformative in healthcare. As technologies continue to advance, PAT could evolve to encompass even more sophisticated analytical techniques, such as terahertz spectroscopy and hyperspectral imaging. The integration of artificial intelligence and machine learning could lead to self-optimizing manufacturing processes, further reducing variability and enhancing efficiency.

Furthermore, PAT's scope could expand beyond pharmaceutical manufacturing into personalized medicine, where real-time monitoring of patients' physiological data could lead to customized treatment regimens. The intersection of PAT with other emerging technologies, such as 3D printing and nanotechnology, could revolutionize drug delivery systems and formulation design[24].

Incorporating PAT into global supply chains might enable real-time tracking of product quality throughout distribution, ensuring that products maintain their intended properties from manufacturing to patient use. This has the potential to enhance patient safety and enable rapid response to supply chain disruptions[25]. The future applications of PAT in Healthcare are listed out in Table 4.

Table 4: Future Applications of PAT in Healthcare

|  |  |
| --- | --- |
| **Future Application of PAT** | **Description** |
| Personalized Medicine | Real-time monitoring for tailored treatment regimens |
| Nanotechnology Integration | Optimized drug delivery systems through real-time analysis |
| Supply Chain Monitoring | Ensuring product quality throughout distribution |
| Artificial Intelligence (AI) | AI-powered self-optimizing manufacturing processes |

.

# CONCLUSION

The convergence of Process Analytical Technology (PAT) and pharmaceutical formulation development marks a paradigm shift in healthcare. Through real-time insights, sensor innovations, data analytics, and Quality-by-Design principles, PAT has revolutionized how pharmaceuticals are created, monitored, and optimized. Challenges in compliance, skills, and integration are being addressed, promising a future of personalized medicine and self-optimizing processes. In this synergy of technology and science, PAT not only shapes pharmaceuticals but also elevates patient care, embodying the spirit of progress in healthcare's evolution.

##### REFERENCES

[1] K. A. Bakeev, Process analytical technology: spectroscopic tools and implementation strategies for the chemical and pharmaceutical industries. John Wiley & Sons, 2010.

[2] W. Chew and P. Sharratt, “Trends in process analytical technology,” Analytical Methods, vol. 2, no. 10, pp. 1412–1438, 2010, doi: 10.1039/c0ay00257g.

[3] M. Fonteyne et al., “Process analytical technology for continuous manufacturing of solid-dosage forms,” TrAC Trends in Analytical Chemistry, vol. 67, pp. 159–166, 2015, doi: 10.1016/j.trac.2015.01.011.

[4] J. Glassey et al., “Process analytical technology (PAT) for biopharmaceuticals,” Biotechnology Journal, vol. 6, no. 4, p. 369, 2011, doi: 10.1002/biot.201000356.

[5] X. Y. Lawrence, R. A. Lionberger, A. S. Raw, R. D’Costa, H. Wu, and A. S. Hussain, “Applications of process analytical technology to crystallization processes,” Advanced drug delivery reviews, vol. 56, no. 3, pp. 349–369, 2004, doi: 10.1016/j.addr.2003.10.012.

[6] A. S. Rathore, M. Yu, S. Yeboah, and A. Sharma, “Case study and application of process analytical technology (PAT) towards bioprocessing: Use of on-line high-performance liquid chromatography (HPLC) for making real-time pooling decisions for process chromatography,” Biotechnology and bioengineering, vol. 100, no. 2, pp. 306–316, 2008.

[7] A. S. El-Hagrasy and J. K. Drennen III, “A process analytical technology approach to near-infrared process control of pharmaceutical powder blending. Part III: quantitative near-infrared calibration for prediction of blend homogeneity and characterization of powder mixing kinetics,” Journal of pharmaceutical sciences, vol. 95, no. 2, pp. 422–434, 2006.

[8] T. R. M. De Beer et al., “Raman spectroscopy as a process analytical technology (PAT) tool for the in-line monitoring and understanding of a powder blending process,” Journal of pharmaceutical and biomedical analysis, vol. 48, no. 3, pp. 772–779, 2008, doi: 10.1016/j.jpba.2008.07.023.

[9] A. A. Gowen, C. P. O’Donnell, P. J. Cullen, G. Downey, and J. M. Frias, “Hyperspectral imaging–an emerging process analytical tool for food quality and safety control,” Trends in food science & technology, vol. 18, no. 12, pp. 590–598, 2007, doi: 10.1016/j.tifs.2007.06.001.

[10] E. K. Read, J. T. Park, R. B. Shah, B. S. Riley, K. A. Brorson, and A. S. Rathore, “Process analytical technology (PAT) for biopharmaceutical products: Part I. Concepts and applications,” Biotechnology and Bioengineering, vol. 105, no. 2, pp. 276–284, 2010.

[11] E. K. Read, R. B. Shah, B. S. Riley, J. T. Park, K. A. Brorson, and A. S. Rathore, “Process analytical technology (PAT) for biopharmaceutical products: Part II. Concepts and applications,” Biotechnology and bioengineering, vol. 105, no. 2, pp. 285–295, 2010.

[12] L. L. Simon et al., “Assessment of recent process analytical technology (PAT) trends: a multiauthor review,” Organic Process Research & Development, vol. 19, no. 1, pp. 3–62, 2015, doi: 10.1021/op500261y.

[13] T. R. M. De Beer et al., “Implementation of a process analytical technology system in a freeze-drying process using Raman spectroscopy for in-line process monitoring,” Analytical chemistry, vol. 79, no. 21, pp. 7992–8003, 2007, doi: 10.1021/ac070549h.

[14] T. R. M. De Beer et al., “In-line and real-time process monitoring of a freeze drying process using Raman and NIR spectroscopy as complementary process analytical technology (PAT) tools,” Journal of pharmaceutical sciences, vol. 98, no. 9, pp. 3430–3446, 2009, doi: 10.1002/jps.21633.

[15] K. H. Esbensen and P. Paasch-Mortensen, “Process sampling: theory of sampling–the missing link in process analytical technologies (PAT),” Process Analytical Technology: Spectroscopic Tools and Implementation Strategies for the Chemical and Pharmaceutical Industries, pp. 37–80, 2010.

[16] K. A. Esmonde-White, M. Cuellar, C. Uerpmann, B. Lenain, and I. R. Lewis, “Raman spectroscopy as a process analytical technology for pharmaceutical manufacturing and bioprocessing,” Analytical and bioanalytical chemistry, vol. 409, no. 3, pp. 637–649, 2017, doi: 10.1007/s00216-016-9824-1.

[17] J. A. Lopes, P. F. Costa, T. P. Alves, and J. C. Menezes, “Chemometrics in bioprocess engineering: process analytical technology (PAT) applications,” Chemometrics and Intelligent Laboratory Systems, vol. 74, no. 2, pp. 269–275, 2004, doi: 10.1016/j.chemolab.2004.07.006.

[18] J. Djuriš, I. Kurćubić, and S. Ibrić, “Review of machine learning algorithms application in pharmaceutical technology,” Archives of Pharmacy, vol. 71, no. Notebook 4, pp. 302–317, 2021.

[19] J. J. Moes, M. M. Ruijken, E. Gout, H. W. Frijlink, and M. I. Ugwoke, “Application of process analytical technology in tablet process development using NIR spectroscopy: Blend uniformity, content uniformity and coating thickness measurements,” International journal of pharmaceutics, vol. 357, no. 1–2, pp. 108–118, 2008, doi: 10.1016/j.ijpharm.2008.01.062.

[20] B. Shrestha, H. Basnett, P. M. Raj, S. S. Patel, M. Das, and N. K. Verma, “Process analytical technology: a quality assurance tool,” Research Journal of Pharmacy and Technology, vol. 2, no. 2, pp. 225–227, 2009.

[21] Z. Munawar, B. Siswoyo, and N. S. Herman, “Machine learning approach for analysis of social media,” ADRI Int. Journal. Information. Technol, vol. 1, no. 1, pp. 5–8, 2017.

[22] N. O’Mahony, T. Murphy, K. Panduru, D. Riordan, and J. Walsh, “Machine learning algorithms for process analytical technology,” in 2016 World Congress on Industrial Control Systems Security (WCICSS), IEEE, 2016, pp. 1–7. doi: 10.1109/WCICSS.2016.7882607.

[23] A. Puranik, P. Dandekar, and R. Jain, “Exploring the potential of machine learning for more efficient development and production of biopharmaceuticals,” Biotechnology Progress, vol. 38, no. 6, p. e3291, 2022, doi: 10.1002/btpr.3291.

[24] M. Tharwat, N. A. Sakr, S. El-Sappagh, H. Soliman, K.-S. Kwak, and M. Elmogy, “Colon cancer diagnosis based on machine learning and deep learning: Modalities and analysis techniques,” Sensors, vol. 22, no. 23, p. 9250, 2022, doi: 10.3390/s22239250.

[25] J. Yuan, C. Chen, W. Yang, M. Liu, J. Xia, and S. Liu, “A survey of visual analytics techniques for machine learning,” Computational Visual Media, vol. 7, pp. 3–36, 2021, doi: 10.1007/s41095-020-0191-7.