Advances in Differential Equations and Control Processes 2026, 33(3), 3800.
doi: https://doi.org/10.59400/adecp3800

Review

Process analytical technology (PAT) and real-time control in chemical manufacturing

Yan Yan

Haixi State Economic Development Research Center, Delingha 817099, China; yan13519785436@163.com

CITATION

Yan Y. Process analytical technology (PAT) and real-time control in chemical manufacturing. Advances in Differential Equations and Control Processes. 2026; 33(3): 3800. https://doi.org/10.59400/adecp3800

ARTICLE INFO

Received: 1 December 2025
Revised: 13 August 2026
Accepted: 27 August 2026
Available online: 24 September 2026

Abstract: Process analytical technology (PAT) has expanded the ability to obtain timely information about manufacturing processes and product-related attributes. However, much of the existing literature focuses on analytical technologies, monitoring applications, or sector-specific implementation, while the connection between PAT measurements, dynamic process models, state estimation, and closed-loop control has received less integrated treatment. This review addresses this gap by examining PAT-enabled real-time manufacturing from a control-oriented perspective across pharmaceutical, chemical, polymer, food, and bioprocess applications. Analytical technologies and their limitations are evaluated together with feedback, feedforward, model predictive control (MPC), nonlinear model predictive control (NMPC), state-estimation methods, and hybrid modelling approaches. A representative dynamic process and MPC framework are also considered to show how measurements, process states, manipulated variables, disturbances, constraints, and quality objectives can be linked within a control system. The reviewed evidence indicates that PAT should not be treated as a control strategy by itself. Its value depends on the reliability of analytical measurements and their integration with suitable models, estimators, and validated control approaches. Implementation maturity varies considerably among industries, with stronger evidence available in pharmaceutical continuous manufacturing and selected crystallisation and process-control applications. Important limitations include calibration transfer, sensor drift, sampling representativeness, plant-model mismatch, model maintenance, validation, and data integration. Emerging AI and digital-twin approaches may extend prediction, estimation, and decision support, but their industrial use remains dependent on reliable data, validated models, and appropriate lifecycle management.

Keywords: process analytical technology (PAT); real-time control; process optimization; model predictive control (MPC); state estimation; hybrid modelling; digital twins; chemical manufacturing

1. Introduction

Modern manufacturing systems require simultaneous management of product quality, process variability, and operational efficiency. Conventional quality-control approaches based primarily on end-product testing remain important for product assessment, but they provide limited information about how process conditions evolve during manufacturing. This limitation has increased interest in analytical and control approaches that provide timely information about process behaviour and support earlier identification and management of process deviations during operation [1,2].

Process analytical technology (PAT) provides a framework for obtaining and interpreting information about manufacturing processes through timely measurement of process variables and quality-related attributes. PAT may incorporate spectroscopic techniques, process sensors, chemometric methods, and other analytical approaches to improve process understanding. However, PAT measurement should be distinguished from process control. Analytical measurements provide information about the process, whereas a control system uses measured or estimated information together with an appropriate control strategy to determine how process inputs should be adjusted. PAT can therefore provide an information layer that supports process modelling, state estimation, and control when integrated with suitable analytical and computational frameworks [3,4].

Substantial literature already addresses PAT and advanced manufacturing from different perspectives. Dickens et al. provided a broad overview of process analysis and PAT [5], while Chanda et al. examined PAT tools and applications in active pharmaceutical ingredient development [6]. Wasalathanthri et al. focused on technologies for real-time monitoring of quality attributes and process parameters in biopharmaceutical development [7], whereas Kim et al. reviewed PAT tools for pharmaceutical unit operations and continuous process verification Kim et al. [8]. A more control-specific perspective was provided by Jelsch et al. [9], who reviewed model predictive control (MPC) in pharmaceutical continuous manufacturing and compared conventional and advanced control strategies. Collectively, these studies provide important foundations for process analysis, analytical monitoring, pharmaceutical implementation, quality management, and process control. However, their primary emphases remain associated with particular analytical technologies, manufacturing sectors, or control applications. Rather than adding another technology-centred overview, the present review adopts a control-oriented perspective to examine how PAT-derived measurements are translated into process information and subsequently incorporated into dynamic models, state-estimation approaches, and advanced control strategies across chemical and related manufacturing systems.

Real-time control is particularly relevant when manufacturing processes exhibit dynamic behaviour, interacting variables, disturbances, and operational constraints. Model-based approaches such as MPC use process representations and available measurements to predict future behaviour and determine control actions while accounting for process limitations. In integrated continuous pharmaceutical manufacturing, plant-wide MPC has been investigated for regulation of critical quality attributes under process uncertainties and disturbances [10]. More recent work has extended model-based control through hybrid process models and nonlinear MPC for continuous manufacturing applications [11]. Hybrid modelling approaches, which combine mechanistic understanding with data-driven information, also provide a means of representing complex processes when purely mechanistic or empirical models are insufficient [12].

The relevance of PAT-enabled monitoring, modelling, and control extends beyond pharmaceutical continuous manufacturing. In polymerisation, analytical measurements and soft-sensor approaches have been investigated for real-time estimation and control of variables that are difficult to measure directly [13]. Fermentation studies have combined spectroscopic and conventional sensor measurements with process monitoring and control frameworks to obtain timely information on biological process behaviour [14]. In specialty chemical batch manufacturing, multivariate statistical approaches have been applied for real-time estimation of process progression and quality-related variables [15]. These applications also illustrate that the role and maturity of PAT-enabled control vary among sectors because measurement requirements, process dynamics, model availability, validation needs, and control objectives are process-specific.

This review, therefore, examines PAT-enabled real-time manufacturing from a control-oriented perspective, with particular attention to the relationship among analytical measurement, data interpretation, dynamic process modelling, state estimation, and advanced control. Analytical technologies and their limitations are first considered as the measurement foundation, followed by real-time control strategies and their mathematical formulation, industrial applications, implementation challenges, representative case evidence, and emerging approaches involving artificial intelligence, digital twins, and connected manufacturing systems. The objective is not to treat PAT and real-time control as interchangeable concepts, but to evaluate how analytical information can become operationally useful when incorporated into appropriate modelling and control frameworks.

Across the literature surveyed in this review, several recurring findings emerge. PAT can improve process visibility and provide timely information for manufacturing decisions, but measurement capability alone does not ensure improved control performance or product quality. The effectiveness of PAT-enabled control depends on analytical reliability, calibration, process-model quality, estimation of difficult-to-measure variables, controller design, system integration, and appropriate validation. The evidence also indicates that implementation maturity differs substantially among manufacturing sectors and that reported benefits cannot be generalized without considering the specific process, measurement strategy, model, control architecture, and validation conditions. Emerging data-driven methods, artificial intelligence, and digital twins may extend prediction, estimation, and decision-support capabilities, but challenges associated with data quality, model transferability, interpretability, lifecycle maintenance, cybersecurity, and regulatory acceptance remain unresolved. The central challenge is therefore not simply the acquisition of more real-time data, but the reliable conversion of analytical measurements into validated process knowledge and control actions under realistic manufacturing conditions.

2. Fundamentals of process analytical technology

Process analytical technology (PAT) has become an important framework for improving process understanding, monitoring manufacturing performance, and supporting quality management in chemical and related industries. Rather than relying exclusively on end-product testing, PAT integrates analytical measurements, process knowledge, and data interpretation approaches to obtain information about critical process behaviour during manufacturing. By providing timely information on process conditions and product-related attributes, PAT can support improved identification of process variability, enhanced decision-making, and more consistent product quality.

The effectiveness of PAT depends on the integration of appropriate analytical technologies, reliable measurement strategies, and suitable data interpretation methods. While PAT provides valuable process information, its contribution to manufacturing improvement depends on measurement reliability, calibration practices, process-specific validation, and the ability to translate analytical information into meaningful operational decisions. This section discusses the fundamental principles of PAT, analytical technologies commonly applied in PAT-enabled manufacturing, and their role in supporting real-time process understanding across different industrial sectors.

2.1. Core principles of process analytical technology

PAT is based on the principle that manufacturing processes can be better understood and controlled by obtaining timely information about process conditions and product quality attributes. The framework combines analytical measurement, process knowledge, and data analysis approaches to support improved understanding of the relationship between process variables and product performance.

A central concept of PAT is the identification of important process variables and quality attributes that influence manufacturing outcomes. However, the relationship between process conditions and product quality is often process-dependent and may involve complex interactions between multiple variables. Therefore, PAT implementation requires not only measurement capability but also appropriate interpretation of analytical information within the context of the specific manufacturing process.

2.1.1. Critical process parameters and critical quality attributes

Critical process parameters (CPPs) are process variables that can influence product quality when their variability affects manufacturing performance. Critical quality attributes (CQAs) represent measurable physical, chemical, biological, or functional characteristics of a product that determine its quality and suitability for intended use.

The relationship between CPPs and CQAs provides the foundation for PAT-based process understanding. For example, in pharmaceutical manufacturing, parameters such as temperature, moisture level, mixing conditions, and residence time may influence CQAs, including active pharmaceutical ingredient distribution, tablet hardness, and dissolution behaviour. In polymer manufacturing, variables such as temperature, monomer concentration, reaction time, and catalyst conditions can affect product characteristics, including molecular weight distribution and polymer properties.

However, CPP–CQA relationships are not universal and depend strongly on process chemistry, equipment configuration, raw material characteristics, and operating conditions. PAT approaches support the identification and monitoring of these relationships by providing analytical information that can improve understanding of process behaviour and facilitate more informed manufacturing decisions [7,16].

Figure 1 illustrates the general PAT framework, showing the relationship between analytical measurements, data interpretation, process understanding, and manufacturing decisions.

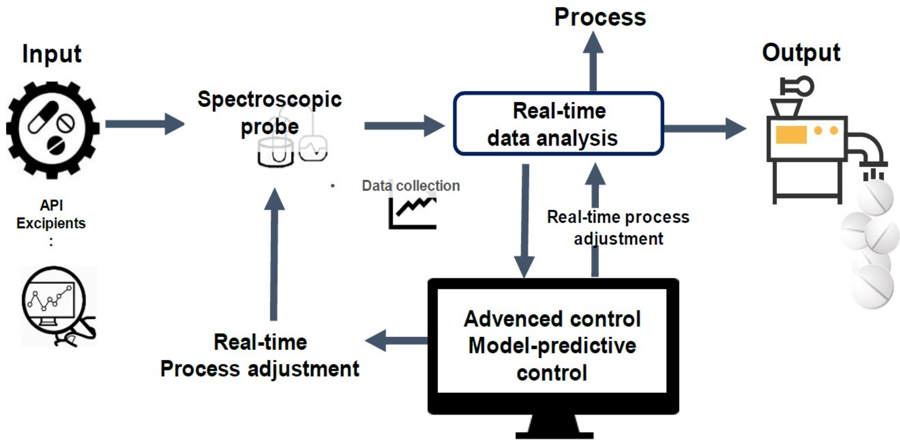

Figure 1. Conceptual framework of PAT-enabled manufacturing, showing the relationship between analytical measurements, data interpretation, process understanding, and subsequent decision-support or control actions [8].

2.1.2. Real-time monitoring

Real-time monitoring is a fundamental capability of PAT because it provides information about process conditions during manufacturing rather than relying solely on post-process analysis. Conventional offline testing remains important for quality assurance; however, it may provide limited information about process evolution and the timing of process deviations.

PAT-based measurements, including spectroscopic techniques and process sensors, can provide continuous or near-real-time information about variables associated with process performance and product quality. For example, near-infrared (NIR) spectroscopy has been applied for monitoring active pharmaceutical ingredient concentration and material properties during pharmaceutical manufacturing processes. The resulting information can support improved assessment of process behaviour and allow earlier identification of deviations compared with conventional sampling approaches [7,17].

Nevertheless, real-time monitoring does not eliminate the need for analytical validation, calibration, or quality assurance procedures. The usefulness of PAT measurements depends on measurement reliability, appropriate data interpretation, and integration with manufacturing objectives.

2.1.3. Process control and optimization

PAT provides analytical information that can support process control and optimization; however, measurement alone does not directly perform control actions. Instead, PAT measurements can be integrated with process models, estimation methods, and control strategies to support operational decisions [18].

In model-based control frameworks, analytical measurements provide information about process behaviour, while mathematical models are used to predict future process conditions and evaluate possible operating adjustments. For example, in polymer manufacturing, measurements of reaction conditions and composition variables can provide information for assessing process behaviour and supporting control strategies aimed at maintaining desired product characteristics.

The application of advanced control approaches such as model predictive control (MPC) requires reliable process models, suitable measurement strategies, and validation under relevant operating conditions. Detailed mathematical formulations of dynamic modelling, state estimation, and predictive control strategies are discussed in Section 3.

2.1.4. Data-driven decision making

PAT systems generate information from multiple analytical instruments, sensors, and process measurements. The interpretation of these data through statistical methods, chemometric models, and data-driven approaches can provide additional understanding of manufacturing behaviour and support decision-making.

For example, combining measurements from particle size analysers, pH sensors, and spectroscopic instruments may provide a more comprehensive assessment of pharmaceutical manufacturing processes. Such information can support detection of process deviations, evaluation of process trends, and improved operational decision-making.

However, data-driven approaches require consideration of data quality, model reliability, and applicability under changing process conditions. The value of PAT data depends not only on the quantity of measurements collected but also on the ability to extract meaningful process information that can support manufacturing objectives [19].

2.2. Technological tools and methods in process analytical technology

The successful implementation of PAT depends on the selection of suitable analytical technologies capable of providing reliable information about process conditions and product characteristics. Different analytical methods provide different levels of chemical specificity, measurement speed, sampling requirements, and suitability for in-line or at-line implementation. Therefore, technology selection depends on the manufacturing process, measurement objectives, required response time, and validation requirements [7,8,20].

Common PAT technologies include spectroscopic methods, chromatographic techniques, mass spectrometry, and process sensors. Each technique provides specific analytical advantages; however, limitations associated with calibration, data interpretation, measurement conditions, and integration requirements must also be considered [7,8,20].

2.2.1. Spectroscopic techniques

Spectroscopic techniques are among the most widely applied analytical methods in PAT because they can provide rapid and non-destructive measurements with limited sample preparation. These techniques are particularly valuable for monitoring chemical composition, material properties, and process changes during manufacturing [4,8,21].

However, spectroscopic methods generally require appropriate calibration models and chemometric approaches to convert spectral information into meaningful process variables. Their performance can be influenced by factors such as sample characteristics, measurement environment, and model transferability between different process conditions [4,8,22].

Near-infrared spectroscopy

Near-infrared spectroscopy is extensively used in PAT applications because it enables rapid measurement of chemical composition and physical properties of materials. NIR has been applied for monitoring moisture content, blend uniformity, and active pharmaceutical ingredient distribution in pharmaceutical manufacturing [4,8,23].

In continuous and batch manufacturing processes, NIR measurements can provide information about material characteristics during operation, allowing improved assessment of process variability. However, NIR measurements typically require robust calibration models, and changes in raw materials, equipment configuration, or operating conditions may affect model performance [4,8,24].

Raman spectroscopy

Raman spectroscopy provides molecular-level information based on vibrational characteristics and is useful for monitoring chemical composition, reaction progress, phase transitions, and crystallization behaviour [8,21].

In pharmaceutical manufacturing, Raman spectroscopy has been investigated for monitoring crystallization processes and identifying changes in solid-state properties. In chemical manufacturing, it can provide information about reaction progression and composition changes [21,25].

Fourier transform infrared spectroscopy

Fourier transform infrared (FTIR) spectroscopy is another important PAT technique for analysing chemical composition and molecular interactions. FTIR has been applied in polymer manufacturing, chemical synthesis, and pharmaceutical processing [7,20].

FTIR measurements can provide information about changes in chemical composition and molecular interactions during processing. However, implementation may require careful consideration of measurement configuration, sample properties, calibration, and environmental effects [7,20].

2.2.2. Chromatographic methods

Chromatographic methods, including high-performance liquid chromatography (HPLC) and gas chromatography (GC), provide high analytical specificity and are widely used for component identification and quantification.

In pharmaceutical manufacturing, chromatography can provide accurate determination of active pharmaceutical ingredient concentration and impurity profiles. These characteristics make chromatographic methods valuable for quality assessment and validation activities.

However, compared with many spectroscopic techniques, chromatographic methods often involve longer analysis times, sample preparation requirements, and greater operational complexity. Therefore, although chromatography provides highly accurate analytical information, its application in real-time PAT frameworks may require integration with rapid analytical approaches or automated sampling systems [26].

2.2.3. Mass spectrometry

Mass spectrometry (MS) provides detailed molecular information by measuring mass-to-charge ratios of chemical species. It is particularly useful for identifying compounds, detecting impurities, and analysing complex reaction systems.

In chemical synthesis, MS can support monitoring of reaction intermediates and product formation. In biopharmaceutical manufacturing, mass spectrometry can contribute to the identification and characterization of impurities and product-related components.

Despite its analytical capability, implementation of MS-based PAT systems may require specialized equipment, technical expertise, and appropriate integration strategies. Therefore, its application is often determined by the required analytical specificity and process monitoring objectives [27].

2.2.4. Process sensors and real-time monitoring devices

Process sensors provide continuous measurements of physical and chemical variables required for understanding manufacturing conditions. Common examples include temperature, pressure, flow, pH, dissolved oxygen, and conductivity measurements.

Sensors are fundamental components of PAT-enabled manufacturing because they provide direct information about process conditions. For example, pH, temperature, and dissolved oxygen sensors are widely used in fermentation processes to monitor biological conditions and support assessment of microbial activity.

However, sensor-based measurements require consideration of calibration, maintenance, drift, and measurement reliability. Sensor performance can directly influence the quality of process information available for monitoring and subsequent decision-making. Therefore, appropriate calibration and maintenance strategies are essential for reliable PAT [18].

Figure 2 provides an overview of representative sensor and analytical modalities used in PAT-enabled manufacturing. **Table 1** presents the comparison of important analytical technologies used in PAT-enabled manufacturing.

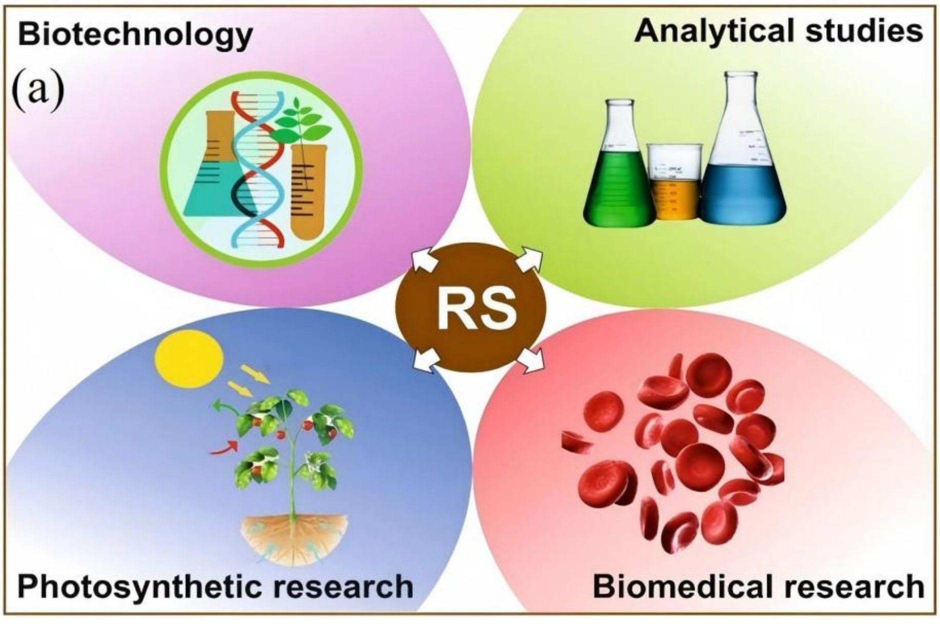

Figure 2. *Cont.*

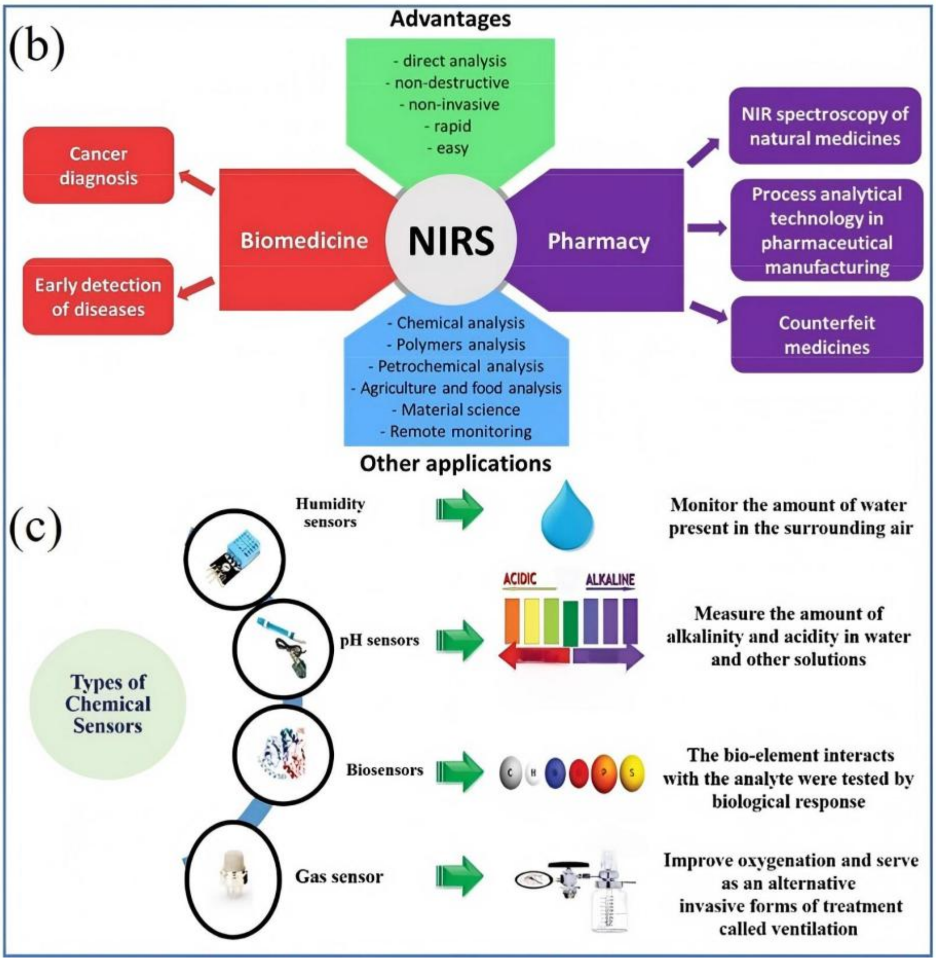

Figure 2. Representative analytical and sensor technologies used for PAT-enabled process monitoring: **(a)** Raman spectroscopy (RS); **(b)** near-infrared spectroscopy (NIRS); **(c)** chemical sensors [28–30].

Table 1. Important analytical technologies used in PAT-enabled manufacturing.

Technology	Description	Typical applications	Advantages	Limitations
NIR spectroscopy	Measures near-infrared absorbance related to chemical composition	API concentration, moisture, blend uniformity	Rapid, non-destructive measurement	Requires calibration models
Raman spectroscopy	Measures molecular vibrations	Reaction monitoring, crystallization, polymerisation	Molecular specificity	Fluorescence and calibration issues
FTIR spectroscopy	Measures infrared absorption associated with chemical bonds	Chemical composition, curing monitoring	Chemical information and process monitoring capability	Measurement configuration limitations
HPLC/GC	Separation and quantification of components	API analysis, impurity measurement	High accuracy and specificity	Longer analysis time and sampling requirements
Mass spectrometry	Molecular mass analysis	Reaction intermediates, impurity detection	Detailed molecular information	Complex implementation
Process sensors	Direct measurement of physical variables	pH, temperature, pressure, dissolved oxygen	Continuous process information	Calibration and drift issues

Note: API: Active pharmaceutical ingredient.

2.2.5. Data acquisition and model-based decision support

PAT implementation requires more than the acquisition of analytical measurements. Data obtained from sensors and analytical instruments must be collected, processed, and interpreted to generate meaningful information about process behaviour. Data acquisition systems, analytical methods, and computational approaches therefore provide the foundation for transforming measurements into usable process information [7,8,12].

The integration of PAT measurements with data processing and modelling approaches enables improved interpretation of complex manufacturing processes. Models may be developed using mechanistic knowledge, empirical relationships, statistical approaches, or combinations of these methods. These models can support estimation of process variables, identification of trends, and improved understanding of relationships between measurements and product quality attributes [7,12].

However, the effectiveness of model-based approaches depends on factors including data quality, measurement reliability, model assumptions, and validation under relevant operating conditions. The mathematical formulation of dynamic process models, state estimation approaches, and predictive control strategies is discussed in Section 3 [7,12].

2.3. Benefits of process analytical technology

The implementation of PAT-enabled manufacturing approaches can provide several potential benefits by improving process understanding, increasing measurement availability, and supporting more informed operational decisions. However, the practical outcomes of PAT depend on factors including measurement reliability, process characteristics, model performance, validation requirements, and successful integration with existing manufacturing systems [7,31].

2.3.1. Improved process understanding and product quality

PAT enables manufacturers to obtain information about process conditions and product-related attributes during manufacturing rather than relying only on end-product testing. By monitoring relevant CPPs and CQAs, PAT approaches can support improved understanding of process variability and assist in maintaining product quality within desired specifications [31,32].

For example, in pharmaceutical manufacturing, PAT measurements can provide information related to active pharmaceutical ingredient distribution, material properties, and process behaviour [4, 7]. However, improvements in product quality depend on appropriate analytical methods, calibration strategies, and validation of the monitoring approach for the specific manufacturing process.

2.3.2. Process optimization

PAT can support process optimization by providing timely information about process behaviour and enabling improved assessment of operating conditions [18,32]. The integration of analytical measurements with modelling and decision-support approaches can help identify process trends, detect deviations, and support optimization strategies.

For example, PAT-based monitoring approaches have been investigated in chemical manufacturing processes where variables such as temperature, composition, and reaction conditions influence product performance [18]. However, claims related to increased yield, reduced energy consumption, or improved efficiency require quantitative evaluation using process-specific studies.

2.3.3. Cost reduction and increased efficiency

By improving process visibility and enabling earlier identification of deviations, PAT has the potential to reduce losses associated with process variability, rework, and inefficient operation. Automated data acquisition and improved process monitoring can also reduce dependence on frequent manual sampling and provide additional support for manufacturing decisions.

Nevertheless, economic benefits depend on implementation factors such as equipment investment, maintenance requirements, process complexity, and the ability to integrate PAT systems with existing manufacturing infrastructure [6,7,31].

2.3.4. Regulatory support and quality management

PAT can support regulatory quality management by providing improved traceability, process knowledge, and access to manufacturing data. In regulated industries such as pharmaceuticals, analytical measurements and data management strategies can contribute to improved process understanding and facilitate documentation of manufacturing performance [8,31].

However, regulatory acceptance requires validated analytical methods, reliable measurement systems, appropriate control strategies, and documented procedures for maintaining system performance throughout the manufacturing lifecycle [7].

2.3.5. Sustainability benefits

PAT approaches may contribute to sustainability objectives by improving resource utilization, reducing unnecessary material consumption, and supporting more efficient operation. Improved monitoring of process conditions can assist in identifying opportunities for reducing waste generation and optimizing resource use [8,18].

For example, real-time monitoring approaches in food and chemical manufacturing may support improved control of process conditions and reduce variability. However, sustainability improvements should be evaluated using appropriate quantitative indicators because environmental benefits depend on process design, operating conditions, and implementation strategy [8].

Overall, PAT represents an important approach for improving process understanding and supporting data-informed manufacturing decisions. By integrating analytical measurements, process knowledge, and computational methods, PAT can contribute to improved product quality, operational efficiency, regulatory support, and sustainability objectives. However, the magnitude of these benefits depends on the reliability of measurements, suitability of analytical methods, robustness of models, and successful integration within specific manufacturing environments.

3. Real-time control systems and model-based process management in chemical manufacturing

Real-time control has become an important component of modern chemical manufacturing because it enables continuous adjustment of operating conditions based on process measurements and system responses. Unlike conventional approaches that rely primarily on periodic sampling and manual intervention, real-time control systems provide continuous information about process behaviour and enable timely corrective actions when deviations occur.

When integrated with process analytical technology (PAT), real-time control approaches provide a pathway for linking analytical measurements with process decision-making. PAT systems provide information about process conditions and product-related attributes, while control strategies use this information to maintain desired operating conditions and improve process performance. However, the effectiveness of real-time control depends on measurement reliability, model accuracy, process understanding, and appropriate validation of the implemented control strategy.

This section discusses the principles of real-time process control, different control strategies used in chemical manufacturing, integration of PAT measurements with control systems, and challenges associated with implementation in industrial environments [33,34].

3.1. Principles of real-time process control

Real-time process control involves the continuous measurement of process variables, interpretation of process behaviour, and adjustment of operating conditions to maintain the process within desired limits. A control system generally consists of measurement devices, data processing components, a control algorithm, and actuators that modify process inputs.

In PAT-enabled manufacturing, analytical measurements provide information about process states that may not be directly observable. These measurements can be integrated with process models and control strategies to estimate process behaviour and determine appropriate operating actions.

A representative source-derived dynamic formulation can be taken from the integrated continuous pharmaceutical manufacturing study of Mesbah et al. [10]. In that study, the plant-wide dynamics were represented by a continuous-time linear state-space model obtained from process data:

$$\dot{x}(t) = Ax(t) + Bu(t) + w(t) \tag{1}$$

$$y(t) = Cx(t) + Du(t) + n(t) \tag{2}$$

where $x(t)$ is the vector of internal process states, $u(t)$ contains manipulated process inputs, and $y(t)$ contains measured process outputs and quality-related variables. The terms $w(t)$ and $n(t)$ represent process and measurement disturbances, respectively, while A, B, C, and D describe the state-space relationships between the process variables. In the continuous pharmaceutical manufacturing application, manipulable critical process parameters were used as control inputs, while critical quality attributes were included among the controlled outputs. Near-infrared measurements provided product-related analytical information, thereby linking the measurement layer with the plant-wide control framework [10].

This formulation illustrates how PAT-enabled measurements can enter a dynamic process representation without treating the analytical instrument itself as the controller. The states describe the evolving internal behaviour of the manufacturing process, manipulated variables provide the degrees of freedom available to the controller, measured outputs provide feedback information, and disturbances represent effects that cannot be completely predicted by the process model.

3.1.1. Feedback loops

Feedback control is one of the most widely implemented approaches in industrial process control. In a feedback system, measured process outputs are compared with desired operating conditions, and corrective actions are applied when deviations occur.

For example, if the temperature of a chemical reactor deviates from the desired operating range, a feedback controller can adjust heating or cooling inputs to return the process to the target condition. Feedback control is particularly effective for reducing the influence of disturbances and maintaining stable operation.

In pharmaceutical manufacturing, feedback strategies can be applied to maintain critical process conditions during operations such as crystallization, drying, or mixing. Maintaining stable temperature conditions during crystallization is important because temperature variations may influence crystal formation and product properties.

Although feedback control provides reliable disturbance rejection, its performance depends on measurement availability and controller design. Because corrective actions occur after deviations are detected, feedback approaches may have limitations when rapid prediction or compensation of future process changes is required [34,35].

3.1.2. Feedforward control

Feedforward control differs from feedback control because it uses information about measurable disturbances to adjust process inputs before deviations occur. Instead of responding only to observed errors, feedforward strategies attempt to anticipate changes in process conditions and compensate accordingly.

For example, in chemical processing, variations in feedstock properties or inlet conditions may influence downstream operation. If such disturbances can be measured or estimated, feedforward control can modify operating parameters in advance to reduce their impact.

Feedforward strategies are therefore valuable when disturbances can be identified and measured [34]. However, their effectiveness depends on the accuracy of disturbance measurements and the relationship between disturbances and process response. In practical manufacturing systems, feedforward approaches are often combined with feedback control to compensate for both predictable and unpredictable process variations. **Figure 3** illustrates a general real-time process control architecture, including process measurement, control computation, and actuator adjustment.

3.1.3. Model predictive control

Model predictive control (MPC) is an advanced control strategy that uses mathematical models to predict future process behaviour and determine optimal control actions while considering process constraints. Unlike conventional feedback approaches that mainly respond to current deviations, MPC evaluates predicted process trajectories over a future time horizon and calculates suitable control actions through an optimization procedure.

MPC is particularly relevant for complex chemical manufacturing processes because many industrial systems involve multiple interacting variables, nonlinear behaviour, and operational constraints. In PAT-enabled manufacturing, analytical measurements provide updated information about process conditions, which can be incorporated into model predictions to improve control decisions.

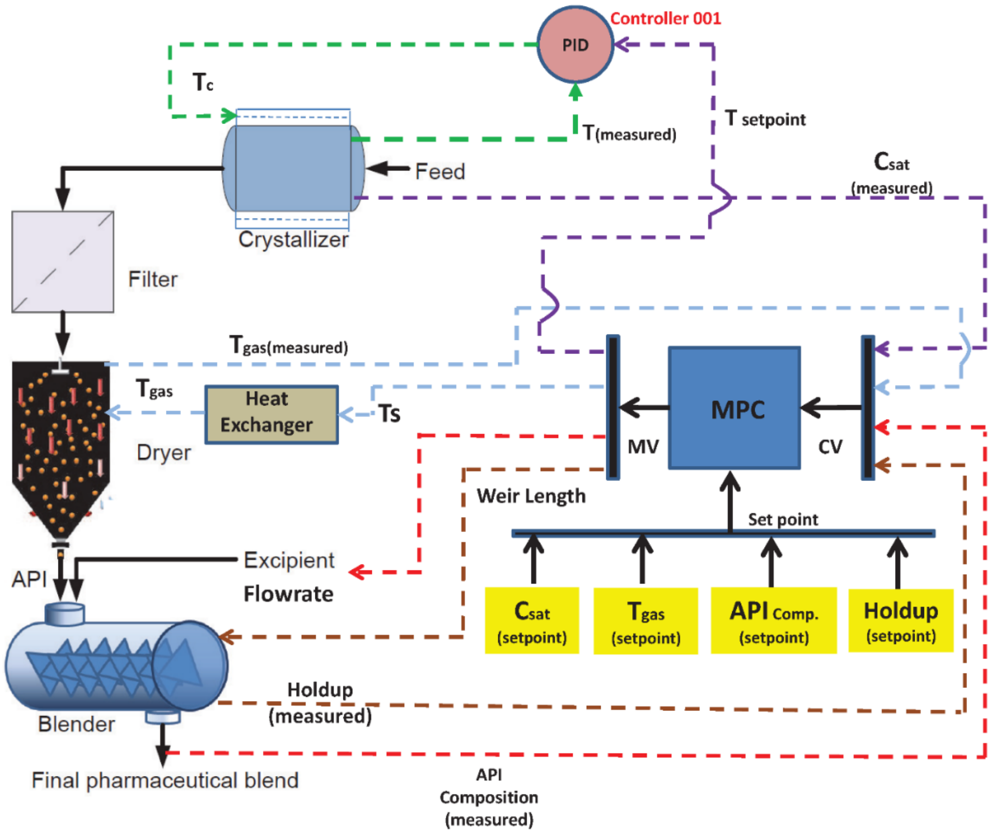

Figure 3. Representative model-based control architecture for continuous pharmaceutical manufacturing [36].

The optimization structure can be illustrated using the plant-wide MPC formulation reported by Mesbah et al. [10]. At each sampling instant k, future changes in the manipulated variables are selected to minimize deviations of predicted outputs from their desired set points while limiting excessive changes in the manipulated inputs:

$$\min_{\Delta u_{\{k|k\}},\cdots,\Delta u_{\{k+N_c-1|k\}}} \sum_{\{i=0\}}^{\{N_p-1\}} ([(y_{\{k+i+1|k\}} - y^{\{SP\}})^{TW})W_y(y_{k+i+1|k} \\ -y^{SP}) + \Delta u_{k+i|k}^{T} W_u \Delta u_{\{k+i|k\}} \tag{3}$$

where N_p is the prediction horizon, N_c is the control horizon, $y_{k+i+1|k}$ represents predicted process outputs, y^{SP} contains the desired output set points, and W_y and W_u weight output deviations and changes in manipulated variables, respectively. The optimization is performed subject to the process prediction model and operating constraints.

In the pharmaceutical pilot-plant implementation, the manipulated critical process parameters were constrained within specified operating bounds:

$$0.8 \leq y_{k+i+1|k} \leq 1.2u_{ss} \tag{4}$$

and an additional upper constraint was imposed on the predicted impurity content:

$$\begin{bmatrix} 0 & 0 & 1 \end{bmatrix} y_{k+i+1|k} \leq \text{IMP}_{max}. \tag{5}$$

These constraints are specific to the application reported by Mesbah et al. [10] and should not be interpreted as universal MPC design limits. Their importance here is that they demonstrate how process operating restrictions and product-quality requirements can be included explicitly within the controller optimization problem. The controller calculates a sequence of future input changes, applies the first control action, obtains updated process measurements, and then repeats the optimization at the next sampling instant. This receding-horizon structure enables the controller to respond to changes in measured process behaviour while retaining explicit consideration of operating constraints [10].

An additional requirement arises when the complete process state cannot be measured directly. In such cases, measured process information is combined with a dynamic model through a state estimator before the estimated states are supplied to the predictive controller. This distinction is important in PAT-enabled manufacturing because analytical measurements may provide only partial information about the internal process state or may provide indirect information about a quality attribute.

Different estimation structures have been investigated in the control literature collected for this review. Huang et al. combined moving horizon estimation with nonlinear model predictive control to update internal state estimates in a pharmaceutical tablet-press system under plant-model mismatch [37]. In a nonlinear continuous stirred tank reactor example, Prakash and Senthil used fuzzy Kalman filtering and augmented-state fuzzy Kalman filtering to estimate reactor states and unmeasured disturbances before supplying these estimates to the NMPC calculation [38]. In their inferential-control example, reactor concentration was estimated from temperature measurements rather than being measured directly. These studies illustrate the control pathway in which available measurements are processed through an estimator, the resulting state estimates are supplied to the dynamic model, and the predictive controller determines the manipulated inputs.

The stability implications of model-based control also require careful distinction between practical closed-loop performance and formal mathematical guarantees. In the integrated pharmaceutical manufacturing study of Mesbah et al. [10], the plant-wide MPC operates above an existing stabilizing regulatory-control layer, and the receding-horizon implementation is used to reduce performance degradation associated with disturbances and model uncertainty. Observer-based NMPC studies similarly demonstrate closed-loop tracking and disturbance-rejection performance using estimated states. However, these application studies do not establish a universal stability or convergence result for PAT-enabled MPC systems. Formal guarantees depend on the process model, estimator properties, controller formulation, constraints, operating region, and assumptions used in the individual design. Consequently, stability and estimator convergence should be evaluated for the specific process and control architecture rather than inferred solely from successful MPC implementation [10, 38].

In practical applications, MPC uses available measurements to update process predictions and determine future control actions while considering system limitations [39, 40]. The quality of MPC performance therefore depends strongly on model accuracy, measurement reliability, and the ability of the model to represent actual process behaviour.

Therefore, MPC implementation requires continuous model evaluation, validation, and maintenance. MPC can use process models and measurements to predict future behaviour and adjust operating conditions, such as feed rates or temperature profiles, to maintain desired polymer characteristics, including molecular weight distribution and viscosity [35, 41].

However, model mismatch remains an important limitation because industrial processes may change due to raw material variation, equipment ageing, or changing operating conditions. Therefore, MPC implementation requires continuous model evaluation, validation, and maintenance.

3.2. Types of real-time control systems

Different types of real-time control systems are applied in chemical manufacturing depending on process complexity, control objectives, available measurements, and operational requirements. These approaches range from conventional feedback controllers used for relatively stable processes to advanced and hybrid control strategies designed for complex systems with multiple interacting variables.

Although control strategies differ in their mathematical formulation and implementation complexity, their common objective is to maintain process operation within acceptable limits while improving stability, efficiency, and product consistency.

3.2.1. Traditional feedback control systems

Traditional feedback control systems, such as proportional-integral-derivative (PID) controllers, remain widely used in industrial manufacturing because of their simplicity, reliability, and practical implementation advantages. These systems continuously compare measured process variables with desired set points and adjust manipulated variables to reduce deviations.

PID controllers are commonly applied in processes where the relationship between process variables is relatively well understood and where rapid correction of disturbances is required. Examples include temperature, pressure, flow, and level control in reactors, heat exchangers, and storage systems.

In food and beverage manufacturing, feedback controllers can be used to regulate temperature during pasteurization processes. Maintaining stable temperature conditions is essential for microbial safety and product quality, and feedback control provides rapid correction when deviations occur [34].

However, conventional feedback systems have limitations when applied to highly nonlinear processes or systems involving multiple interacting variables. Because they primarily respond to observed deviations, they may provide limited predictive capability when future process changes need to be anticipated.

3.2.2. Advanced process control systems

Advanced process control (APC) systems extend conventional feedback approaches by incorporating process models, optimization methods, and multivariable control strategies. These systems are particularly useful for complex manufacturing processes where several variables interact and where operating constraints must be considered simultaneously.

Model predictive control (MPC) is one of the most widely applied APC approaches in industrial processes. By using mathematical models to predict future process behaviour, MPC can determine suitable operating adjustments while considering process limitations.

In biopharmaceutical manufacturing, for example, process variables such as temperature, pH, dissolved oxygen, and nutrient concentration interact to influence cell growth and product formation. Advanced control approaches can assist in maintaining suitable operating conditions and reducing variability in complex biological processes [39,42].

Despite these advantages, APC implementation requires reliable models, sufficient process knowledge, and appropriate validation. The performance of advanced control systems may decrease when process behaviour changes significantly from the conditions used during model development.

3.2.3. Hybrid control systems

Hybrid control systems combine multiple control approaches, such as feedback, feedforward, model-based control, and data-driven methods, to address limitations associated with individual strategies.

These approaches are particularly relevant for manufacturing processes where both predictable relationships and uncertain process behaviours exist. Mechanistic models can provide process understanding, while data-driven approaches can capture complex relationships that may not be fully represented by conventional models.

Hybrid approaches may combine process models with real-time measurements to improve control performance in chemical reactors or other complex manufacturing systems. In such systems, feedback control can provide stability, feedforward control can compensate for measurable disturbances, and model-based methods can support prediction and optimization.

However, hybrid systems introduce additional complexity because multiple models, data sources, and control strategies must be integrated and maintained. Successful implementation, therefore, requires appropriate model validation, data quality management, and computational capability [40,43].

3.3. Real-time control in process analytical technology: Integration and benefits

The integration of PAT measurements with real-time control systems provides a framework for linking analytical information with manufacturing decisions. PAT technologies generate measurements related to process conditions and product attributes, while control systems use this information to adjust operating conditions and maintain desired process performance [7,44].

In PAT-enabled control frameworks, analytical measurements provide process information that is interpreted through data analysis and modelling approaches to improve process understanding. This information is then used to support control decisions and implement appropriate adjustments to manufacturing conditions [11,44].

This integration can improve process visibility, support earlier detection of deviations, and enable more consistent manufacturing operations. However, the benefits achieved depend on measurement reliability, model performance, control strategy design, and validation of the complete system [7,11,44].

3.3.1. In pharmaceutical manufacturing

In pharmaceutical manufacturing, PAT measurements such as near-infrared and Raman spectroscopy can provide information about material properties, composition, and process behaviour during manufacturing operations [8,21].

When integrated with model-based control approaches, these measurements can support improved monitoring of critical process parameters and critical quality attributes. For example, PAT measurements can provide information about blend uniformity or active pharmaceutical ingredient distribution, which can support process decisions during continuous manufacturing [11,44].

The effectiveness of such systems depends on analytical calibration, model reliability, and appropriate integration with manufacturing control strategies [7, 44]. Detailed pharmaceutical applications and industrial examples are discussed further in Sections 4 and 6.

3.3.2. In petrochemical manufacturing

Petrochemical manufacturing involves complex processes with multiple interacting variables, including temperature, pressure, composition, and flow conditions. PAT-enabled monitoring approaches can provide additional information about process behaviour and product characteristics [35,45].

When combined with advanced control strategies, analytical measurements can support improved operation of processes such as distillation and polymer production by enabling better assessment of process conditions [13,46,47].

However, implementation requires reliable measurements, appropriate process models, and consideration of the operational complexity of large-scale industrial systems [35,46]. Specific petrochemical applications are discussed in later sections.

3.3.3. In food and beverage manufacturing

Food and beverage processes, including fermentation and thermal processing, often involve dynamic conditions where variations in temperature, pH, oxygen availability, and composition influence product quality. Real-time measurements from sensors and analytical instruments can provide information about process behaviour, while control strategies can adjust operating conditions to maintain desired performance. Fermentation processes may use measurements of variables such as pH, dissolved oxygen, and metabolites to support process monitoring and control decisions. However, biological variability and measurement challenges remain important considerations during implementation [48–50].

3.4. Challenges in implementing real-time control

Although real-time control provides significant opportunities for improving manufacturing performance, its industrial implementation involves technical, operational, and economic challenges. These challenges are related not only to control algorithms but also to process understanding, data availability, system integration, and long-term maintenance.

3.4.1. Complexity of process models

Developing reliable process models is one of the major challenges in implementing advanced real-time control systems. Chemical and biological manufacturing processes often exhibit nonlinear behaviour, changing operating conditions, and complex interactions between variables.

Model inaccuracies can reduce control performance because control decisions depend on the ability of models to represent actual process behaviour. Potential approaches for addressing this challenge include hybrid modelling combining mechanistic knowledge and experimental data, adaptive models that update with new process information, and improved state estimation methods [35, 40]. However, maintaining model accuracy throughout the manufacturing lifecycle remains a critical requirement.

3.4.2. Integration with existing systems

Many manufacturing facilities contain legacy equipment and control infrastructures that were not originally designed for PAT-enabled real-time control. Integration challenges may include compatibility between analytical instruments and existing control systems, communication protocols, hardware modifications, and validation requirements. Possible solutions include modular implementation approaches, gradual system upgrades, and improved integration frameworks. However, implementation must consider the technical and economic feasibility of upgrading existing manufacturing systems [34].

3.4.3. Data management and analysis

Real-time control systems generate large amounts of information from sensors, analytical instruments, and process models. Effective use of this information requires reliable data acquisition, processing, storage, and interpretation. Challenges include maintaining data quality, synchronizing information from different sources, managing uncertainty in analytical measurements, and ensuring reliable communication between systems. Data management strategies, including advanced analytics and appropriate data validation procedures, are therefore essential for maintaining reliable control performance [51].

3.4.4. Cost and return on investment considerations

Implementation of real-time control systems requires investment in analytical equipment, software infrastructure, computational resources, and personnel training. Although these systems may provide long-term benefits through improved efficiency, reduced variability, and better quality management, economic justification depends on the specific manufacturing context. Factors influencing return on investment

(ROI) include process scale, product value, implementation complexity, maintenance requirements, and expected operational improvements. Therefore, economic evaluation should consider the complete lifecycle cost rather than only initial implementation expenses [31,34].

Real-time control represents an important component of modern chemical manufacturing by enabling dynamic adjustment of operating conditions based on process information. When integrated with PAT, control systems provide a pathway for linking measurement, modelling, and operational decisions. However, successful implementation requires reliable analytical measurements, appropriate modelling approaches, effective data management, and consideration of technical and economic constraints [34,52].

4. Applications of process analytical technology and real-time control

The integration of process analytical technology (PAT) with real-time control approaches has expanded the capability of manufacturing industries to monitor process behaviour, evaluate quality-related attributes, and support more informed operational decisions. PAT provides analytical information about critical process variables and quality attributes, while real-time control strategies use this information to maintain process operation within desired conditions. These approaches have been investigated across the pharmaceutical, chemical, petrochemical, food, and bioprocess industries, where improved process understanding and management of variability are essential. This section discusses key applications of PAT and real-time control, focusing on the relationship between analytical measurements, modelling approaches, and process control implementation [32].

4.1. Chemical manufacturing processes

Chemical manufacturing processes are complex and dynamic, involving interactions among multiple process variables that influence product characteristics and operational performance. Effective monitoring and control of critical process parameters (CPPs) are therefore important for maintaining consistent manufacturing conditions. PAT approaches provide analytical information about process behaviour and quality-related attributes, while real-time control strategies use this information to support operational decisions and maintain processes within desired conditions. These approaches can be applied in both continuous and batch manufacturing environments [32,53].

4.1.1. Continuous chemical processes

Continuous chemical production requires stable operation because variations in feed conditions, temperature, pressure, flow rate, and composition can influence product characteristics. Real-time monitoring of these variables is important for maintaining process stability and consistent product quality. PAT techniques such as NIR and Raman spectroscopy can provide information on chemical composition and reaction behaviour during operation. When integrated with modelling approaches and control strategies such as model predictive control (MPC), these measurements can support adjustment of operating variables and improve process understanding.

In polymerisation processes, spectroscopic measurements have been investigated for monitoring reaction progress, monomer concentration, and polymer-related characteristics. The combination of PAT measurements with predictive models can support estimation of process states and assist in maintaining desired polymer properties under changing operating conditions [13,45,47].

4.1.2. Batch chemical processes

Batch manufacturing is widely used for fine chemicals, pharmaceutical intermediates, and specialty products where controlling reaction conditions is essential for achieving consistent product properties. PAT measurements can provide information on process evolution and quality-related variables throughout the batch, allowing improved process understanding and earlier identification of process deviations compared with conventional offline analysis.

In batch processes, analytical measurements can be combined with statistical models, soft sensors, and advanced control strategies to support process monitoring and operational decision-making. Successful implementation depends on measurement reliability, appropriate modelling approaches, and validation of the monitoring strategy for the specific manufacturing process [15,31,32].

4.2. Pharmaceutical industry

The pharmaceutical sector is one of the most developed application areas for PAT and real-time control because of strict quality requirements and the need for consistent manufacturing performance. PAT approaches provide information about process variables and quality-related attributes, while real-time control strategies use this information to support process regulation and quality management [4,31].

4.2.1. Tablet manufacturing

Tablet manufacturing requires control of important quality attributes, including API distribution, blend uniformity, moisture content, tablet hardness, and dissolution behaviour. PAT tools such as NIR and Raman spectroscopy can provide real-time analytical information related to these attributes and can be combined with chemometric models for process monitoring.

When integrated with feedback control or model-based control strategies, PAT measurements can support adjustment of process variables such as mixing, granulation, and drying conditions. These approaches improve process visibility and support more consistent tablet manufacturing by enabling earlier assessment of process behaviour [4,31].

4.2.2. Biopharmaceutical manufacturing

Biopharmaceutical manufacturing involves complex biological systems in which cell growth, metabolism, nutrient availability, and environmental conditions influence process performance and product quality. PAT tools such as Raman spectroscopy, near-infrared spectroscopy, and other online analytical technologies have been investigated for monitoring process variables and quality-related information.

When combined with chemometric models, soft sensors, and predictive approaches, PAT measurements can support estimation of difficult-to-measure variables and improve understanding of biological process behaviour. These approaches provide information that can support monitoring and future integration with advanced control strategies [7,54,55].

4.3. Petrochemical industry

The petrochemical industry involves large-scale manufacturing processes for producing chemicals derived from petroleum and natural gas feedstocks, including polymers and other chemical intermediates. These processes involve complex interactions among operating variables, reaction conditions, and product characteristics, requiring effective monitoring and control strategies. PAT approaches have been investigated in petrochemical applications to provide information on chemical composition, process behaviour, and quality-related variables, while real-time control strategies can use this information to support operational decisions [32].

4.3.1. Refining and distillation

Refining and distillation operations require monitoring of variables such as temperature, pressure, flow rate, and composition to maintain stable operation and product specifications. PAT approaches, including spectroscopic techniques, can provide information about chemical composition and process behaviour during operation. When integrated with process models and control strategies, these measurements can support improved process monitoring and adjustment of operating conditions [32,34].

4.3.2. Polymer production

Polymerisation is an important process in petrochemical manufacturing where variables such as temperature, pressure, monomer concentration, and catalyst conditions influence polymer characteristics. PAT techniques such as Raman and NIR spectroscopy can provide real-time information about reaction behaviour and composition during polymer production. When combined with chemometric models, soft sensors, or advanced control strategies, these measurements can support estimation of process states and adjustment of operating conditions to maintain desired polymer properties [13,45,47].

4.4. Food and beverage industry

The food and beverage industry includes diverse manufacturing processes such as fermentation, brewing, and food processing, where product quality depends on raw material characteristics, biological activity, and process conditions. PAT approaches provide opportunities for monitoring critical process variables and quality-related attributes, while real-time control strategies can support adjustment of operating conditions based on process information.

4.4.1. Fermentation processes

Fermentation processes require monitoring of variables such as temperature, pH, dissolved oxygen, nutrient availability, and microbial activity because these factors influence biological process behaviour and product characteristics. PAT tools, including spectroscopy and online sensors, can provide information about fermentation states and support predictive modelling approaches. When integrated with data-driven models and control strategies, these measurements can assist in maintaining suitable operating conditions and improving process understanding [49,56].

4.4.2. Quality control in food processing

In food processing applications, PAT techniques such as NIR spectroscopy can provide rapid information about composition and quality-related attributes of raw materials and products. These measurements can be integrated with process monitoring systems to support control of operating conditions such as temperature and moisture during manufacturing. The effectiveness of such approaches depends on calibration quality, measurement reliability, and appropriate integration with production systems [57,58].

PAT and real-time control approaches provide a framework for improving process monitoring and supporting manufacturing decisions across multiple industrial sectors. Their effectiveness depends on the availability of reliable analytical measurements, appropriate modelling approaches, and successful integration with control systems. While applications differ according to process characteristics and quality objectives, a common principle is the transformation of analytical information into actionable process knowledge that supports improved manufacturing control [56,59].

5. Challenges in implementing process analytical technology and real-time control

The integration of process analytical technology (PAT) and real-time control systems into chemical manufacturing provides opportunities to improve process understanding, enhance monitoring capability, and support more consistent manufacturing operations. However, successful implementation requires addressing several technical, operational, regulatory, economic, and organizational challenges. These challenges include compatibility with existing manufacturing infrastructure, reliability of analytical measurements, management of complex process data, regulatory validation requirements, investment considerations, and workforce readiness. This section discusses the major barriers associated with PAT and real-time control implementation and highlights practical approaches that can support successful adoption. A summary of the major benefits and persistent challenges associated with PAT and real-time control implementation across industrial settings is provided in **Table 2**.

Table 2. Benefits and challenges of implementing PAT and real-time control.

Aspect	Potential benefits	Challenges
Product Quality	Improved process understanding, enhanced monitoring of quality attributes, and improved consistency through informed process decisions	Sensor calibration, analytical method reliability, and integration with manufacturing systems
Process Efficiency	Improved process visibility, earlier detection of deviations, and potential reduction of process variability	High implementation complexity and difficulty demonstrating long-term benefits
Regulatory Support	Improved traceability and data availability to support quality management activities	Validation, documentation, and compliance with regulatory expectations
Economic Performance	Potential reduction in process variability, rework, and resource consumption	High initial investment and uncertainty in return on investment

Table 2. *Cont.*

Aspect	Potential benefits	Challenges
Sustainability	Potential improvement in resource utilization through optimized operation	Data infrastructure limitations and integration challenges

5.1. Technical and operational challenges

Technical and operational challenges represent some of the primary barriers to implementing PAT and real-time control systems. These challenges are associated with integrating analytical technologies into existing manufacturing environments, maintaining measurement reliability, and ensuring that process information can be effectively converted into operational decisions.

5.1.1. Integration with legacy systems

Many chemical manufacturing facilities rely on established production equipment and control architectures that were not originally designed to accommodate advanced PAT measurements or real-time control frameworks. Integrating these technologies may require modifications to existing infrastructure, additional instrumentation, and compatibility assessment between analytical systems and process control platforms. For example, implementation of real-time monitoring in pharmaceutical tablet manufacturing may require upgrades to existing mixing and granulation systems because older equipment may lack suitable sensors for monitoring variables such as moisture or particle-related attributes. Practical approaches include phased implementation, modular PAT integration, and targeted equipment upgrades to reduce disruption to existing operations [60].

5.2. Analytical measurement reliability: Calibration, drift, and maintenance

PAT and real-time control systems depend on reliable analytical measurements to provide accurate information for process monitoring and decision-making. Sensor drift, calibration errors, environmental effects, and maintenance requirements can reduce measurement reliability and negatively influence control performance. For example, inaccurate temperature or concentration measurements in chemical reactors may result in inappropriate control actions and affect product quality. Therefore, regular calibration, performance monitoring, and maintenance strategies are essential for maintaining analytical reliability and ensuring that PAT systems continue to provide suitable process information [7,34].

5.2.1. Complexity of data integration and management

PAT and real-time control systems generate large volumes of data from multiple analytical instruments, sensors, and control platforms. Converting these heterogeneous data sources into meaningful process information remains a significant challenge, particularly for manufacturing systems involving multiple interacting variables. For example, biopharmaceutical processes may require integration of information from cell culture measurements, including pH, temperature, dissolved oxygen, and nutrient concentrations, together with spectroscopic measurements. Effective data management strategies are required to ensure reliable data processing, interpretation, and availability for real-time decision-making [18].

5.3. Data consistency and integration across systems

Manufacturing environments commonly include multiple analytical and control systems that generate data with different formats, frequencies, and levels of uncertainty. Ensuring consistent data integration across these systems is essential because inaccurate or poorly synchronized information may affect process monitoring and control decisions. For example, pharmaceutical manufacturing may involve combining measurements from techniques such as HPLC, NIR spectroscopy, and other sensors to assess process and quality attributes. Effective integration of analytical information is therefore required to support reliable real-time decision-making [7,23].

5.4. Regulatory and compliance issues

Regulatory considerations represent a critical factor in the adoption of PAT and real-time control systems, particularly in highly regulated industries such as pharmaceuticals and biopharmaceuticals. PAT and real-time control systems can provide improved process understanding and support quality management strategies; however, regulatory acceptance requires validated analytical methods, reliable control strategies, appropriate documentation, and lifecycle management of analytical and modelling approaches. Although regulatory frameworks encourage improved process understanding and advanced manufacturing approaches, PAT implementation does not automatically guarantee compliance. Manufacturers must demonstrate that analytical methods, control strategies, and data systems are appropriately validated, reliable, and suitable for their intended application.

5.4.1. Food and Drug Administration guidelines for process analytical technology

The Food and Drug Administration (FDA) process analytical technology framework provides guidance for applying analytical measurements and process understanding approaches to pharmaceutical manufacturing. However, successful implementation requires manufacturers to demonstrate the accuracy, reliability, and traceability of PAT systems through appropriate validation and documentation procedures. Regulatory acceptance depends not only on the analytical technology itself but also on evidence that the measurement strategy and associated control approach can consistently support product quality objectives [31].

5.4.2. Validation and documentation

Validation and documentation requirements represent significant considerations during PAT implementation. Analytical systems, models, and control strategies must be evaluated to demonstrate that they provide reliable information and perform consistently under intended operating conditions. In regulated manufacturing environments, this includes establishing appropriate validation procedures, maintaining data integrity, and ensuring that system performance remains acceptable throughout the manufacturing lifecycle [7, 31]. For model-based PAT and control strategies, lifecycle management is also required to maintain model performance when process conditions, raw materials, equipment configuration, or operating ranges change.

5.5. Cost and return on investment considerations

Implementation of PAT and real-time control systems often requires substantial investment in analytical equipment, software infrastructure, integration activities, and personnel training. Although these technologies may provide long-term benefits through improved monitoring and reduced process variability, the economic justification depends strongly on process characteristics, manufacturing scale, and the ability to quantify operational improvements [31].

5.5.1. High initial capital costs

Implementation of PAT and real-time control systems may require substantial initial investment in analytical instruments, process sensors, control hardware, software, system integration, and personnel training. The relative burden of these costs depends on manufacturing scale, existing infrastructure, analytical requirements, and the extent of modifications needed to integrate new technologies into established production systems. Smaller manufacturing facilities may face greater difficulty justifying such investments when expected operational benefits are uncertain or difficult to quantify.

5.5.2. Justifying the return on investment

Demonstrating the return on investment of PAT and real-time control systems can be difficult because economic benefits may arise from several interacting factors, including reduced process variability, improved process visibility, decreased rework, improved quality management, and more efficient resource utilization. Quantifying these benefits requires consideration of both implementation costs and operational performance over the system lifecycle. The economic justification, therefore, depends on process scale, product value, implementation complexity, maintenance requirements, and the magnitude of measurable manufacturing improvements [3,18,61].

5.6. Cultural and organizational barriers

Cultural and organizational factors can influence the successful implementation of PAT and real-time control systems, in addition to technical, regulatory, and economic considerations. Adoption may be limited by resistance to changes in established operating practices, insufficient understanding of new analytical and control technologies, and shortages of personnel with appropriate interdisciplinary expertise.

5.6.1. Resistance to change

Implementation of PAT and advanced control systems may require changes in established manufacturing practices, operator responsibilities, and decision-making procedures. Resistance can occur when expected benefits are not clearly demonstrated or when personnel are concerned about changes to established workflows. Appropriate implementation strategies, therefore, include communication of system objectives, involvement of relevant stakeholders during deployment, and training that enables personnel to understand and use the new analytical and control capabilities.

5.6.2. Lack of skilled personnel

PAT-enabled manufacturing requires expertise across analytical chemistry, process engineering, data analysis, modelling, automation, and control. Developing and maintaining this interdisciplinary capability can be difficult, particularly when advanced approaches such as MPC, soft sensing, or data-driven modelling are introduced into existing manufacturing environments. Workforce development and targeted technical training are therefore important components of long-term implementation. **Table 3** summarises the major challenges associated with implementing PAT and real-time control systems and presents corresponding mitigation strategies that can support successful industrial adoption. The relationship between process understanding, PAT-based monitoring and control, continuous process verification, technology transfer, and real-time release testing is illustrated in **Figure 4**.

Table 3. Challenges in implementing PAT and real-time control with proposed mitigation strategies.

Challenge	Description	Proposed mitigation
Integration with legacy systems	Existing infrastructure may not support advanced PAT measurements or control strategies	Phased implementation, modular integration, and targeted equipment upgrades
Analytical measurement reliability	Sensor drift, calibration requirements, and maintenance affect data reliability	Routine calibration, performance monitoring, and maintenance strategies
Data management and integration	Multiple analytical and control systems generate complex data streams	Development of suitable data architectures and analytical processing frameworks
Regulatory validation	PAT systems require evidence of accuracy, reliability, and traceability	Alignment with regulatory expectations, validation procedures, and lifecycle management
High implementation cost	Significant investment may be required for equipment, software, and training	Pilot studies, cost-benefit evaluation, and staged deployment

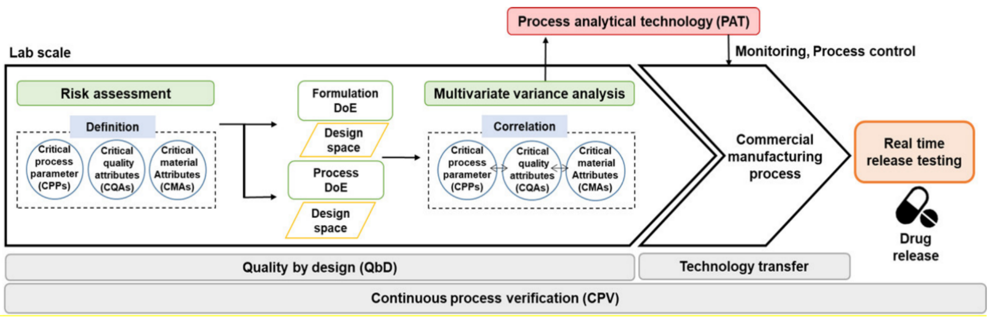

Figure 4. Relationship between PAT, quality by design, continuous process verification, technology transfer, and real-time release testing in pharmaceutical manufacturing [8].

Figure 4 qualitatively maps how PAT-enabled real-time control contributes to sustainability metrics such as energy efficiency, waste reduction and resource utilization. The implementation of PAT and real-time control systems offers important opportunities to improve process understanding and manufacturing performance, but successful adoption requires coordinated consideration of technical, regulatory, economic, and organizational factors. Addressing challenges associated with analytical reliability, data management, validation, infrastructure compatibility, and workforce capability is essential for sustainable deployment. Although implementation barriers can be significant, appropriately designed PAT and control strategies can support more consistent, efficient, and better-controlled manufacturing operations [7,34,62].

Despite these challenges, successful applications of PAT and real-time control have been reported across multiple manufacturing sectors. The following section presents representative case studies illustrating how these technologies have been applied to improve process understanding and support manufacturing decisions.

6. Case studies and real-world examples

The integration of process analytical technology (PAT) and real-time control approaches has become an important strategy for improving process understanding and supporting more consistent manufacturing operations. By providing timely information on process variables and quality-related attributes, PAT-enabled approaches can support monitoring, modelling, and decision-making across different manufacturing sectors. This section presents representative case studies from pharmaceutical, petrochemical, food and beverage, specialty chemical, and biopharmaceutical applications to illustrate how PAT measurements and real-time control frameworks have been investigated for addressing process variability, improving operational visibility, and supporting quality management.

6.1. Case study 1: Pharmaceutical industry real-time control in tablet manufacturing

Pharmaceutical manufacturing requires strict control of critical process parameters (CPPs) and critical quality attributes (CQAs) to ensure consistent product quality and regulatory compliance [8, 63]. In conventional tablet manufacturing, important quality characteristics such as active pharmaceutical ingredient concentration, tablet hardness, dissolution behaviour, and moisture content are often assessed through offline analytical testing. Although these approaches provide essential quality assurance, they may provide limited information about process evolution during operation. Therefore, PAT-enabled monitoring approaches have been increasingly investigated to provide timely process information and support improved process understanding and control decision-making.

Continuous pharmaceutical manufacturing has become an important application area for PAT-enabled real-time monitoring and control because it requires consistent regulation of process conditions and product quality attributes during operation. Published studies on continuous tablet manufacturing have investigated the integration of PAT measurements with process monitoring and control strategies to provide information on process behaviour and support quality management. These studies provide a more traceable basis for evaluating how analytical measurements can contribute to real-time manufacturing decisions compared with traditional batch sampling approaches.

In continuous tablet manufacturing, PAT measurements can provide real-time information related to process variables and quality attributes, but these measurements do not directly perform process control. Instead, analytical information can be integrated with process models, estimation methods, and advanced control strategies to support operating decisions [64]. In this framework, model predictive control approaches use process models to predict future behaviour and determine appropriate control actions while considering process constraints [60].

Reported pharmaceutical manufacturing studies demonstrate that PAT-enabled monitoring and model-assisted control approaches can improve process visibility and support more consistent operation of continuous manufacturing systems. However, the extent of improvement depends on factors including analytical measurement reliability, model accuracy, process variability, and validation requirements. Therefore, successful implementation requires not only appropriate PAT technologies and control algorithms but also robust calibration strategies, model maintenance procedures, and integration with existing manufacturing systems.

NIR spectroscopy was applied for real-time monitoring of API concentration during the granulation process, providing analytical information on process behaviour during continuous manufacturing. The resulting measurements were integrated with a model predictive control (MPC) framework to support prediction of process evolution and adjustment of operating conditions [37].

6.2. Case study 2: Petrochemical industry real-time control in polymerization

Polymerisation represents a highly dynamic process in chemical manufacturing, where variations in operating conditions such as temperature, pressure, reactant concentration, and catalyst activity can significantly influence polymer characteristics, including molecular weight distribution, viscosity, and mechanical properties. Because many quality-related variables are not directly measurable during operation, real-time monitoring and process analytical approaches have been investigated to improve process understanding and support more consistent polymer production. Reported applications in polymerisation systems have demonstrated the use of analytical measurements and model-based approaches for monitoring process behaviour and managing variability under changing operating conditions.

PAT techniques such as Raman and near-infrared spectroscopy can provide real-time information related to polymer composition, reaction progress, and process-state variables during polymerization [45,47]. When integrated with predictive models or advanced control strategies, including soft-sensor approaches for real-time monitoring and control of polymerisation processes [13], these measurements can support improved process monitoring and decision-making. In model-based control frameworks, analytical measurements provide information that can be used to estimate process behaviour and determine appropriate adjustments to operating variables, such as operating conditions and process inputs relevant to the specific polymerisation system. The effectiveness of this approach depends on the accuracy of the process model, reliability of analytical measurements, and the ability to maintain model performance under varying operating conditions.

The integration of PAT measurements with model-based monitoring or control strategies has demonstrated potential for improving polymerisation process understanding and maintaining product quality consistency. By providing information on reaction behaviour and product-related characteristics, PAT-enabled approaches can support more informed operating decisions and help reduce variability in polymer properties [13, 45, 47]. However, reported benefits such as reductions in scrap, energy consumption, or production costs should be evaluated on the basis of specific process studies and quantitative performance comparisons, as implementation outcomes depend strongly on reactor design, control objectives, measurement reliability, and operating conditions.

6.3. Case study 3: Food and beverage industry real-time control in fermentation

Fermentation represents an important production process in the food and beverage industry, including applications such as brewing, dairy fermentation, and production of bio-based food ingredients. These processes are highly dynamic and sensitive to variations in temperature, pH, dissolved oxygen concentration, nutrient availability, and microbial activity, which can influence product characteristics and process performance. Because fermentation behaviour changes continuously and many quality-related variables cannot be directly measured using conventional approaches, PAT-enabled monitoring strategies have been investigated to provide timely process information and improve understanding of fermentation dynamics.

PAT tools, including dissolved oxygen and pH sensors as well as spectroscopic techniques such as near-infrared and Raman spectroscopy, can provide real-time information about fermentation states and product-related variables [14, 65]. Spectroscopic and sensor-based approaches have been investigated for fermentation monitoring and prediction, including digital and model-based approaches for fermentation control [49]. Spectroscopic measurements combined with chemometric or predictive models have been investigated for estimating important fermentation characteristics and supporting process monitoring. When integrated with appropriate modelling and control frameworks, PAT-derived information can contribute to improved operational decisions by enabling better assessment of process behaviour and adjustment of relevant operating conditions. However, implementation requires reliable calibration, robust models, and consideration of biological variability between fermentation systems.

Applications of PAT in fermentation demonstrate the potential of real-time monitoring approaches to improve process visibility and support more consistent operation of biological production systems. Continuous measurements of fermentation variables can provide information for process analysis, quality management, and future integration with advanced control strategies. Nevertheless, specific benefits such as improved product uniformity, reduced waste, or reduced energy consumption should be evaluated using individual process studies with quantitative performance comparisons, as outcomes depend on fermentation type, process objectives, measurement strategy, and control implementation.

6.4. Case study 4: Specialty chemicals industry real-time monitoring in batch processing

Specialty chemicals are frequently manufactured using batch processes because these production routes provide flexibility for high-value products, including fine chemicals, intermediates, and advanced materials. However, batch processes can exhibit significant variability due to changes in reaction conditions, raw material characteristics, and operating parameters. Variables such as temperature, reaction time, pressure, and composition can influence final product properties, making reliable monitoring and quality assessment important for achieving consistent production.

Industrial specialty chemical batch processes often face challenges associated with limited real-time visibility of process evolution and product quality. Conventional offline sampling and laboratory analysis can provide important quality information but may delay the detection of process deviations. Faggian et al. demonstrated an industrial fed-batch specialty chemical case where multivariate statistical techniques were applied for real-time estimation of process progression and product quality variables, improving monitoring capability compared with conventional sampling approaches [15].

PAT and data-driven monitoring approaches can provide additional information about batch-process behaviour by combining process measurements with analytical or statistical models. In specialty chemical manufacturing, real-time monitoring frameworks can estimate process conditions and quality-related variables, allowing earlier identification of deviations and supporting more informed operational decisions [15, 66]. While advanced control strategies can further extend these capabilities, their implementation requires appropriate process models, reliable measurements, and validation for the specific manufacturing system.

The application of real-time monitoring approaches in specialty chemical batch manufacturing has demonstrated potential benefits such as improved process understanding, faster identification of deviations, and reduced dependence on extensive offline sampling. However, broader claims related to increased yield, reduced scrap rates, or cost savings require quantitative validation through specific industrial studies because outcomes depend on process characteristics, control objectives, and implementation conditions.

6.5. Biopharmaceutical industry

Biopharmaceutical manufacturing involves highly complex biological systems in which variations in cell growth, nutrient availability, metabolism, and environmental conditions can influence product quality and process performance. Unlike many chemical manufacturing processes, bioprocesses involve dynamic biological behaviour that can make direct prediction and control of critical quality attributes (CQAs) challenging. Consequently, process analytical technology (PAT) approaches have been increasingly investigated to provide real-time information on critical process parameters (CPPs), improve process understanding, and support more consistent biopharmaceutical production [7, 54].

A range of PAT tools have been applied in biopharmaceutical manufacturing, including Raman spectroscopy, near-infrared spectroscopy, biocapacitance measurements, and other online analytical technologies. Raman spectroscopy has become particularly important for upstream bioprocess monitoring because it can provide in-line measurements of metabolites and process variables when combined with multivariate calibration models. Similarly, spectroscopic sensors integrated with chemometric approaches can transform complex analytical signals into information relevant for process monitoring and decision-making [54, 67].

In biopharmaceutical manufacturing, PAT measurements are increasingly combined with soft sensors, predictive models, and advanced data analytics to estimate difficult-to-measure variables and support process control strategies. Soft sensors integrate process measurements with mathematical models to predict target variables, enabling real-time monitoring of CQAs and CPPs when direct measurement is difficult or impractical. These model-based approaches provide a pathway from analytical measurement to process decision-making and can support improved monitoring and predictive process management [68, 69].

Applications of PAT in biopharmaceutical manufacturing have demonstrated the potential to improve process visibility, enable earlier detection of process deviations, and support more consistent product quality management. However, implementation remains challenging because of biological variability, model maintenance requirements, regulatory validation, data integrity considerations, and the need to demonstrate robustness across different scales and manufacturing conditions. Therefore, successful PAT-enabled bioprocess control requires integration of reliable analytical technologies, validated models, and appropriate manufacturing control strategies [54, 69].

The case studies presented in this section illustrate how PAT and real-time monitoring approaches can support improved process understanding across different manufacturing sectors. Although the specific technologies and objectives differ among pharmaceutical, petrochemical, food and beverage, specialty chemical, and biopharmaceutical applications, a common principle is the integration of reliable measurements with modelling and decision-support frameworks. The practical benefits of these approaches depend on process-specific validation, measurement reliability, model robustness, and successful integration with existing manufacturing systems. **Table 4** summarises the representative case studies discussed in this section, highlighting the applied PAT technologies, modelling and control strategies, evidence-supported contributions, and key implementation challenges.

Table 4. Representative industrial applications of PAT-enabled monitoring and model-based control approaches across different manufacturing sectors, highlighting applied PAT technologies, modelling strategies, evidence-supported contributions, and implementation challenges.

Industry sector	Process/ Application	PAT measurements	Modelling/Control strategy	Evidence-supported contribution	Implementation considerations	References
Pharmaceutical	Continuous tablet manufacturing	NIR spectroscopy and other PAT measurements for monitoring API concentration, blend/process behaviour, and quality-related attributes	Process models and advanced control approaches, including MPC frameworks	Real-time process monitoring, improved process understanding, and support for quality management decisions	Measurement reliability, model validation, calibration strategy, regulatory requirements	Huang et al. [37], Singh et al. [60], Pauli et al. [64]
Petrochemical	Polymerisation process monitoring	Raman, NIR, and other spectroscopic measurements for polymer process monitoring	Chemometric models, soft sensors, and control-oriented modelling approaches	Real-time monitoring of polymerisation behaviour and estimation of process/product-related variables	Model robustness, sensor calibration, transferability between processes	Gonzaga et al. [13], Fischer et al. [45], Santos et al. [47]
Food and beverage	Fermentation process monitoring	pH, dissolved oxygen, spectroscopic measurements including NIR/Raman approaches	Predictive models, digital twins, and model-based monitoring/control frameworks	Improved understanding of fermentation dynamics and support for process prediction and decision-making	Biological variability, model calibration, process-specific validation	Cervera et al. [14], Zhao et al. [49], Müller et al. [65]
Specialty chemicals	Batch process monitoring	Process measurements combined with analytical and multivariate monitoring methods	Multivariate statistical models and data-driven monitoring approaches	Real-time estimation of process behaviour and quality-related variables; reduced dependence on extensive offline analysis	Model maintenance, validation, process-specific implementation requirements	Faggian et al. [15], Sartori [66]

Table 4. *Cont.*

Industry sector	Process/ Application	PAT measurements	Modelling/Control strategy	Evidence-supported contribution	Implementation considerations	References
Biopharmaceutical	Upstream bioprocess monitoring and control	Raman spectroscopy, near-infrared spectroscopy, biocapacitance measurements, and online analytical technologies	Chemometric models, soft sensors, predictive models, and data-driven monitoring approaches	Real-time monitoring of CPPs/CQAs, improved process understanding, and support for process decision-making	Biological variability, model maintenance, regulatory validation, data integrity, and scale transfer	Esmonde-White et al. [54], Claßen et al. [67], Rathore et al. [68], Sathiyapriyan et al. [69]

7. Future trends and developments

Rapid advances in analytical technologies, computational methods, and digital manufacturing approaches are expected to influence the future development of process analytical technology (PAT) and real-time control systems in chemical manufacturing. Current PAT frameworks have improved process understanding by enabling real-time monitoring of critical process parameters (CPPs) and critical quality attributes (CQAs); however, further progress is required to achieve more adaptive, predictive, and robust manufacturing systems. Future developments are expected to involve improvements in sensor technologies, advanced data analytics, artificial intelligence (AI), digital twins, and Industry 4.0-based manufacturing architectures (**Table 5**).

Table 5. Future trends, contributions, and remaining challenges in PAT-enabled real-time control.

Trend	Description	Contribution to PAT and real-time control	Remaining challenges
Advanced Sensor Technologies	Development of miniaturized, smart, and advanced analytical sensors for improved process measurements	Improved availability, sensitivity, and reliability of real-time measurements to support process monitoring, state estimation, and control decisions	Sensor calibration stability, measurement uncertainty, lifecycle management, and validation under industrial operating conditions
Industry 4.0 and Industrial Internet of Things (IIoT) Integration	Connection of analytical instruments, sensors, control systems, and manufacturing platforms through digital communication networks	Enhanced data availability, improved process visibility, and integration of PAT information with manufacturing systems	Interoperability between heterogeneous systems, cybersecurity, data integrity, and integration with existing infrastructure
Edge Computing and Distributed Data Processing	Processing analytical and process data closer to the point of generation rather than relying only on centralized systems	Reduced communication delays and improved responsiveness for real-time monitoring and control applications	Computational limitations, secure data communication, validation of distributed processing architectures
Artificial Intelligence and Machine Learning	Application of data-driven models for prediction, anomaly detection, soft sensing, and process optimization	Improved prediction of process behaviour, estimation of difficult-to-measure variables, and support for advanced decision-making	Data quality, model interpretability, uncertainty quantification, transferability between processes, and regulatory acceptance
Digital Twin Technology	Integration of process models, real-time data, and analytical information to create dynamic representations of manufacturing systems	Enhanced process understanding, predictive analysis, optimization support, and predictive maintenance capabilities	Model accuracy, continuous model updating, computational requirements, and lifecycle management
Sustainable PAT-Enabled Manufacturing	Application of monitoring and control strategies to improve resource utilization and reduce waste generation	Improved energy efficiency, reduced material losses, and support for sustainable manufacturing practices	Quantification of sustainability benefits, process-specific evaluation, and balancing economic and environmental objectives

Although these technologies provide significant opportunities for improving process monitoring and control, their industrial adoption remains dependent on addressing unresolved challenges associated with measurement reliability, data quality, model transferability, validation requirements, cybersecurity, and regulatory acceptance. Therefore, future PAT-enabled manufacturing systems will require not only technological advancement but also reliable integration of analytical measurements, process models, and control strategies to ensure robust operation under changing manufacturing conditions [7,8,32].

7.1. Advances in sensor technology

PAT-enabled manufacturing depends strongly on the availability of reliable analytical measurements. Future developments in sensor technology are expected to improve measurement sensitivity, selectivity, robustness, and integration capability, enabling broader application of real-time monitoring approaches. Advances in miniaturized sensors, smart sensing platforms, and biological and chemical sensors may provide improved access to process information, particularly for complex manufacturing environments where conventional measurement approaches remain challenging [7,44].

However, future sensor development is not limited to improving measurement capability alone. Industrial implementation requires sensors that maintain reliable performance under variable operating conditions, provide stable calibration over extended operation, and generate data suitable for integration with modelling and control frameworks. Sensor reliability, calibration transfer, and lifecycle management remain important considerations because inaccurate measurements can directly affect model predictions and control decisions.

7.1.1. Miniaturization of sensors

Miniaturization of analytical devices represents an important direction for future PAT development because smaller and more integrated sensors may enable wider deployment of real-time monitoring systems. Portable and compact analytical devices could facilitate measurements in smaller-scale manufacturing systems, laboratory-scale processes, and distributed production environments where conventional analytical equipment may be difficult to implement.

For example, miniaturized spectroscopic devices based on technologies such as near-infrared and Raman spectroscopy may support more flexible PAT implementation by reducing equipment size and enabling measurements closer to the process location. However, miniaturization must also address challenges associated with analytical performance, calibration stability, and validation before widespread industrial adoption [70].

7.1.2. Smart sensors

Smart sensors that combine sensing capability, local data processing, and communication functions are expected to become increasingly important in PAT-enabled manufacturing systems. These sensors can improve data availability by enabling faster processing and communication between measurement devices and manufacturing control platforms.

In future manufacturing environments, smart sensors may support more distributed monitoring architectures by providing process information closer to the point of measurement. However, increased sensor connectivity also introduces challenges related to data integrity, cybersecurity, interoperability, and validation, particularly in regulated manufacturing environments. Therefore, the adoption of smart sensor networks requires consideration of both technological capability and system reliability [71].

7.1.3. Biological and chemical sensors

Advanced biological and chemical sensors are expected to contribute significantly to future PAT applications, particularly in biopharmaceutical and food manufacturing processes where biological variability and complex reaction pathways create challenges for conventional monitoring approaches.

Improved sensing technologies may provide additional information about biological activity, contamination risks, and process conditions, supporting improved monitoring and decision-making. However, successful implementation requires reliable analytical performance, appropriate validation strategies, and integration with process models capable of interpreting complex biological measurements [7,50].

Improved sensing technologies may provide additional information about biological activity, contamination risks, and process conditions, supporting improved monitoring and decision-making. However, successful implementation requires reliable analytical performance, appropriate validation strategies, and integration with process models capable of interpreting complex biological measurements.

7.2. Integration with Industry 4.0 and the Internet of Things

The integration of PAT with Industry 4.0 frameworks and the Industrial Internet of Things (IIoT) represents an important future direction for chemical manufacturing. Connected sensing systems, distributed data platforms, and advanced communication architectures can improve the availability and accessibility of process information, enabling more integrated monitoring and decision-support capabilities.

In future PAT-enabled manufacturing environments, IIoT approaches may allow analytical instruments, process sensors, control systems, and manufacturing information platforms to exchange information more efficiently. This connectivity can support improved process visibility and facilitate integration between PAT systems and manufacturing execution systems (MES), enterprise resource planning (ERP) platforms, and other digital manufacturing infrastructures.

However, increased connectivity also introduces important technical and operational challenges. These include interoperability between heterogeneous systems, cybersecurity risks, data integrity management, and the need for appropriate validation strategies in regulated manufacturing environments. Therefore, the future development of IIoT-enabled PAT systems will require not only improved connectivity but also reliable data governance and secure integration with existing manufacturing infrastructures [72].

7.2.1. Increased connectivity and data sharing

The increasing connectivity of analytical instruments, sensors, and manufacturing systems provides opportunities for improved data availability and more integrated process management. Future PAT architectures may incorporate distributed sensing networks in which information from multiple process locations can be combined to improve process understanding and support advanced monitoring strategies.

For example, integration of PAT data with digital manufacturing platforms may enable more effective coordination between process monitoring, quality management, and production planning activities. However, achieving these capabilities requires addressing challenges associated with data standardization, communication protocols, and reliable transfer of information between different manufacturing systems.

In particular, large-scale deployment of connected PAT systems requires consideration of cybersecurity, system compatibility, and long-term maintenance of digital infrastructures [72].

7.2.2. Edge computing

Edge computing is an emerging approach within Industry 4.0 architectures that involves processing data closer to the point of generation rather than transferring all information to centralized computing platforms. In PAT-enabled manufacturing, edge computing may reduce communication delays and enable faster interpretation of process measurements, which can be beneficial for applications requiring rapid process responses.

For example, processing analytical data locally at the sensor or equipment level may allow faster detection of process deviations and support more responsive control actions. However, implementation of edge-based PAT architectures requires consideration of computational limitations, data validation, cybersecurity, and appropriate integration with existing control systems [73].

7.3. Artificial intelligence and machine learning in process control

Artificial intelligence (AI) and machine learning (ML) are among the most significant emerging technologies influencing the future development of PAT and real-time control systems. These approaches provide opportunities to extract additional information from complex process data, develop predictive models, improve process monitoring, and support advanced decision-making.

Within PAT-enabled manufacturing, AI and ML approaches may complement conventional mechanistic modelling by identifying complex relationships between process measurements and quality-related outcomes. Applications include soft sensors, anomaly detection, predictive analytics, and optimization of nonlinear manufacturing systems.

However, industrial implementation of AI-based approaches remains challenging because of limitations related to data availability, model interpretability, uncertainty quantification, validation, and transferability between different manufacturing conditions. Therefore, future AI-enabled control systems are expected to require integration between data-driven methods, process knowledge, and established control frameworks rather than complete replacement of mechanistic approaches [19,74].

7.3.1. Predictive analytics

Machine learning-based predictive analytics has the potential to improve PAT-enabled manufacturing by estimating process behaviour, identifying deviations, and predicting quality-related outcomes before problems occur. These approaches are particularly relevant for complex chemical and biological processes where relationships between measurable process variables and product attributes may be nonlinear or difficult to describe using conventional models.

In bioprocessing, AI-based approaches have been investigated for predicting process behaviour using measurements such as pH, temperature, dissolved oxygen, and metabolite concentrations. Such predictive capabilities may support improved feeding strategies, process optimization, and more effective monitoring of biological variability.

Furthermore, data-driven models can contribute to the development of soft sensors for estimating difficult-to-measure variables, thereby improving the availability of process information for monitoring and control applications [74, 75].

7.3.2. Self-learning systems

Self-learning and adaptive AI systems represent a potential future direction for improving the flexibility of real-time process control. Unlike static models that require manual redevelopment when process conditions change, adaptive approaches may update their predictions using newly acquired process information.

Such capabilities may be valuable in manufacturing environments where raw materials, equipment conditions, or operating ranges vary over time. However, fully autonomous decision-making remains challenging in regulated manufacturing because AI-based systems must maintain reliability, transparency, and compliance with validation requirements.

Therefore, future self-learning systems are expected to function primarily as adaptive decision-support tools integrated with established control frameworks, rather than replacing human oversight and validated process control strategies [19, 74].

7.3.3. Optimization of complex processes

AI and ML approaches have been increasingly investigated for optimization of complex manufacturing processes involving multiple interacting variables. These approaches can analyse large process datasets to identify operating patterns, predict process responses, and support optimization strategies that may be difficult to achieve using conventional modelling approaches alone.

In chemical manufacturing, AI-based optimization methods may support processes where variables such as temperature, composition, reaction conditions, and product properties interact in complex ways. When combined with process knowledge and control frameworks, these approaches may improve optimization capability while maintaining consideration of physical constraints and manufacturing requirements.

However, successful industrial application requires reliable training data, appropriate model validation, and mechanisms to ensure that AI-based recommendations remain consistent with process constraints and quality requirements [19, 74].

7.4. Digital twins and simulation in real-time control

Digital twin technology represents an emerging approach for integrating process models, real-time data, and analytical information to improve monitoring, prediction, and decision-making in manufacturing systems. Unlike conventional process simulations that are typically developed for offline analysis, digital twins aim to provide dynamic representations of physical systems by continuously incorporating information from sensors and operational data.

In PAT-enabled manufacturing, digital twins may provide a framework for combining analytical measurements with process models to improve process understanding and support advanced control strategies. By integrating real-time measurements with predictive models, digital twins can assist in evaluating process behaviour, identifying potential deviations, and supporting optimization activities.

However, the industrial implementation of digital twins remains dependent on several technical factors, including model accuracy, availability of reliable process data, computational requirements, and continuous updating of model performance throughout the manufacturing lifecycle. Therefore, digital twins should be considered as complementary tools that enhance PAT and control capabilities rather than replacing validated process models and control strategies [76, 77].

7.4.1. Simulating process behavior

Digital twins can support process simulation by enabling manufacturers to evaluate potential operating scenarios before implementing changes in the physical process. This capability may be valuable during process development, scale-up activities, and optimization of complex manufacturing operations.

Digital twins can be used to investigate the influence of changes in operating conditions, equipment performance, or material properties on process behaviour. When combined with PAT measurements, these virtual representations may improve understanding of process dynamics and support more informed control decisions.

Nevertheless, reliable simulation depends strongly on the quality of the underlying process models and the availability of representative operational data. Maintaining model accuracy when process conditions change remains an important challenge for future digital twin applications [76].

7.4.2. Predictive maintenance

Predictive maintenance is another important application area of digital twin technology. By combining equipment models with historical and real-time operational data, digital twins may support early identification of equipment degradation and assist maintenance planning.

In chemical manufacturing, digital representations of equipment such as pumps, valves, and heat exchangers may use information such as temperature, vibration, and pressure measurements to evaluate equipment condition. Such approaches can potentially reduce unexpected downtime by supporting maintenance decisions before equipment failure occurs.

However, predictive maintenance models require reliable data, appropriate failure prediction methods, and continuous validation to ensure that predictions remain accurate under changing operating conditions. Therefore, future implementation will depend on integration between digital models, sensor networks, and industrial maintenance strategies [78].

7.5. Sustainability and green manufacturing

Sustainability has become an increasingly important objective in chemical manufacturing, with industries seeking to improve resource efficiency, reduce environmental impacts, and comply with evolving environmental requirements. PAT and real-time control approaches can contribute to these objectives by improving process understanding, reducing variability, and enabling operation closer to desired conditions.

Future developments in sustainable manufacturing are expected to involve improved integration of analytical measurements, process models, and optimization strategies to support more efficient use of energy, materials, and resources. However, quantifying sustainability improvements remains challenging because benefits depend on process characteristics, operating conditions, and system boundaries used for evaluation [79, 80].

7.5.1. Energy efficiency

Real-time monitoring and control strategies may contribute to improved energy efficiency by enabling manufacturers to maintain operation closer to optimal conditions. By continuously evaluating process variables, control systems can adjust operating parameters such as temperature, pressure, flow rates, and heating or cooling requirements.

Improved monitoring and control of drying operations may support better adjustment of temperature and airflow according to product conditions, reducing unnecessary energy consumption while maintaining product quality.

However, achieving measurable energy reductions requires appropriate process models, reliable measurements, and careful evaluation of overall process performance. Energy improvements should therefore be assessed within the context of the complete manufacturing system rather than individual operating variables alone [79, 80].

7.5.2. Waste reduction

PAT-enabled monitoring and control approaches may contribute to waste reduction by improving early detection of process deviations and reducing the occurrence of off-specification products. Continuous monitoring of process conditions can provide earlier information about abnormal operation, allowing corrective actions before significant material losses occur.

In food, pharmaceutical, and chemical manufacturing, improved process understanding may support more efficient use of raw materials and reduce unnecessary reprocessing or disposal. However, the magnitude of waste reduction depends on the specific manufacturing process, implementation strategy, and effectiveness of the associated control approach.

Therefore, future developments should focus not only on improving monitoring capability but also on demonstrating measurable sustainability benefits through appropriate process evaluation methods [8]. The future development of PAT and real-time control systems in chemical manufacturing will be shaped by advances in analytical technologies, data-driven modelling, artificial intelligence, digital twin frameworks, and sustainable manufacturing approaches. These developments provide opportunities to improve process understanding, enhance predictive capability, and support more adaptive control strategies by integrating real-time measurements with advanced computational methods. However, successful industrial implementation will depend on addressing remaining challenges associated with measurement reliability, data quality, model validation, regulatory acceptance, and long-term operational robustness. Therefore, future PAT-enabled manufacturing systems are expected to evolve toward integrated frameworks in which analytical measurements, process models, state estimation methods, and advanced control strategies operate together to support reliable and efficient manufacturing. The major technological trends and associated implementation challenges are summarized in **Table 5** [7, 18, 81].

8. Conclusion

This review examined process analytical technology (PAT) and real-time manufacturing from a control-oriented perspective, focusing on how analytical measurements can be translated into process understanding, state estimates, and control actions. One clear conclusion is that PAT and real-time control should not be treated as the same concept. PAT provides timely information about the process, but the value of that information depends on how effectively it is combined with suitable models, estimators, and control strategies.

The reviewed studies show that PAT becomes particularly useful when it is integrated with model-based control. Approaches such as model predictive control and nonlinear model predictive control can account for interacting variables, process constraints, and quality objectives, while state estimators, observers, soft sensors, and hybrid models can help when important process variables cannot be measured directly. At the same time, the success of these approaches still depends on reliable measurements, suitable models, effective controller design, and the ability to deal with disturbances and plant-model mismatch.

he level of implementation also varies across industries. Pharmaceutical Tcontinuous manufacturing provides some of the strongest examples of integrated PAT and advanced control, while relevant applications have also been reported in crystallisation, polymerisation, fermentation, specialty chemicals, and biopharmaceutical processing. However, results from one application cannot be transferred directly to another because process dynamics, measurement requirements, regulatory expectations, and existing infrastructure differ considerably.

Several challenges remain unresolved, including sensor drift, calibration transfer, sampling limitations, model maintenance, state estimation under uncertainty, validation, and long-term control robustness. Future work should therefore place greater emphasis on robust and adaptive control, reliable state estimation, model lifecycle management, uncertainty assessment, and quantitative industrial validation. AI and digital-twin approaches may further support prediction and decision-making, but their use still requires careful attention to interpretability, cybersecurity, validation, and maintenance.

This review is also limited by its broad cross-industry scope and by the uneven availability of detailed quantitative and mathematical evidence across sectors. Overall, the literature suggests that progress in PAT-enabled manufacturing will depend less on collecting more real-time data and more on converting reliable measurements into validated process knowledge and effective control decisions.

Funding: This work received no external funding.

Institutional review board statement: Not applicable.

Informed consent statement: Not applicable.

Data availability statement: All data is included within the article.

Conflict of interest: The author declares no conflict of interest.

AI use statement: The author declares that no artificial intelligence (AI) tools were used in the preparation of this manuscript.

References

1. Chen Z, Lovett D, Morris J. Process analytical technologies and real time process control a review of some spectroscopic issues and challenges. Journal of Process Control. 2011; 21(10): 1467–1482.
2. Sacher S, Poms J, Rehrl J, et al. PAT implementation for advanced process control in solid dosage manufacturing—A practical guide. International Journal of Pharmaceutics. 2022; 613: 121408.
3. Munson J, Freeman Stanfield C, Gujral B. A Review of Process Analytical Technology (PAT) in the USA Pharmaceutical Industry. Current Pharmaceutical Analysis. 2006; 2(4): 405–414.
4. Laske S, Paudel A, Scheibelhofer O, et al. A review of PAT strategies in secondary solid oral dosage manufacturing of small molecules. Journal of Pharmaceutical Sciences. 2017; 106(3): 667–712.
5. Dickens JE. Overview of Process Analysis and PAT. In: Bakeev KA (editor). Process Analytical Technology: Spectroscopic Tools and Implementation Strategies for the Chemical and Pharmaceutical Industries. John Wiley & Sons, Ltd.; 2010.
6. Chanda A, Daly AM, Foley DA, et al. Industry perspectives on process analytical technology: Tools and applications in API development. Organic Process Research & Development. 2015; 19(1): 63–83.
7. Wasalathanthri DP, Rehmann MS, Song Y, et al. Technology outlook for real-time quality attribute and process parameter monitoring in biopharmaceutical development—A review. Biotechnology and Bioengineering. 2020; 117(10): 3182–3198.
8. Kim EJ, Kim JH, Kim MS, et al. Process Analytical Technology Tools for Monitoring Pharmaceutical Unit Operations: A Control Strategy for Continuous Process Verification. Pharmaceutics. 2021; 13: 919. doi: 10.3390/pharmaceutics13060919
9. Jelsch M, Roggo Y, Kleinebudde P, et al. Model predictive control in pharmaceutical continuous manufacturing: A review from a user's perspective. European Journal of Pharmaceutics and Biopharmaceutics. 2021; 159: 137–142.
10. Mesbah A, Paulson JA, Lakerveld R, et al. Model Predictive Control of an Integrated Continuous Pharmaceutical Manufacturing Pilot Plant. Organic Process Research & Development. 2017; 21(6): 844–854.
11. Huang YS, Lagare RB, Bailey P, et al. Hybrid model development and nonlinear model predictive control implementation for continuous dry granulation process. Computers & Chemical Engineering. 2024; 183: 108586.
12. Sansana J, Joswiak MN, Castillo I, et al. Recent trends on hybrid modeling for Industry 4.0. Computers & Chemical Engineering. 2021; 151: 107365.
13. Gonzaga JCB, Meleiro LAC, Kiang C, et al. ANN-based soft-sensor for real-time process monitoring and control of an industrial polymerization process. Computers & Chemical Engineering. 2009; 33(1): 43–49.
14. Cervera AE, Petersen N, Lantz AE, et al. Application of near-infrared spectroscopy for monitoring and control of cell culture and fermentation. Biotechnology Progress. 2009; 25(6): 1561–1581.
15. Faggian A, Facco P, Doplicher F, et al. Multivariate statistical real-time monitoring of an industrial fed-batch process for the production of specialty chemicals. Chemical Engineering Research and Design. 2009; 87(3): 325–334.
16. Yenduri G, Costa AP, Xu X, et al. Impact of critical process parameters and critical material attributes on the

critical quality attributes of liposomal formulations prepared using continuous processing. International Journal of Pharmaceutics. 2022; 619: 121700.
17. Igne B, Ciurczak EW. Near-Infrared Spectroscopy in the Pharmaceutical Industry. In: Ozaki Y, Huck C, Tsuchikawa S, et al. (editors). Near-Infrared Spectroscopy: Theory, Spectral Analysis, Instrumentation, and Applications. Springer; 2020. pp. 391–412.
18. Bakeev AK (editor). Process Analytical Technology: Spectroscopic Tools and Implementation Strategies for the Chemical and Pharmaceutical Industries. John Wiley & Sons, Ltd.; 2010. pp. 1–15.
19. He QP, Wang J. Statistical process monitoring as a big data analytics tool for smart manufacturing. Journal of Process Control. 2018; 67: 35–43.
20. Seenivasan R, Pachiyappan JK, Vivek Reddy M, et al. A systematic review: Exploration of process analytical technology techniques (PAT) and their multifaceted advantages in industrial processes. International Journal of Applied Pharmaceutics. 2024; 16(2): 44–51.
21. Nagy B, Farkas A, Borbás E, et al. Raman spectroscopy for process analytical technologies of pharmaceutical secondary manufacturing. AAPS PharmSciTech. 2018; 20(1): 1.
22. Galata DL, Domokos A, Démuth B, et al. In-line indirect concentration measurement of ultralow dose API during twin-screw wet granulation based on NIR and Raman spectroscopy. International Journal of Pharmaceutics. 2024; 664: 124650.
23. Rosas JG, Blanco M, GonzÃ¡lez JM, et al. Real-time determination of critical quality attributes using near-infrared spectroscopy: A contribution for process analytical technology (PAT). Talanta. 2012; 97: 163–170.
24. Miyano T, Nakagawa H, Watanabe T, et al. Operationalizing Maintenance of Calibration Models Based on Near-Infrared Spectroscopy by Knowledge Integration. Journal of Pharmaceutical Innovation. 2015; 10(4): 287–301.
25. Steinbach D, Anderson CA, McGeorge G, et al. Calibration Transfer of a Quantitative Transmission Raman PLS Model: Direct Transfer vs. Global Modeling. Journal of Pharmaceutical Innovation. 2017; 12(4): 347–356.
26. Siddique I. Unveiling the power of high-performance liquid chromatography: Techniques, applications, and innovations. European Journal of Advances in Engineering and Technology. 2021; 8(9): 79–84.
27. Reemtsma T. Determination of molecular formulas of natural organic matter molecules by (ultra-) high-resolution mass spectrometry: Status and needs. Journal of Chromatography A. 2009; 1216(18): 3687–3701.
28. Allakhverdiev ES, Khabatova VV, Kossalbayev BD, et al. Raman Spectroscopy and Its Modifications Applied to Biological and Medical Research. Cells. 2022; 11: 386. doi: 10.3390/cells11030386
29. Kos J, Pavelek D, Kaykhaii M, et al. Unveiling the transformative power of near-infrared spectroscopy in biomedical and pharmaceutical analysis: Trends, advancements, and applications. European Journal of Pharmaceutical Sciences. 2025; 212: 107175.
30. Inobeme A, Natarajan A, Pradhan S, et al. Chemical Sensor Technologies for Sustainable Development: Recent Advances, Classification, and Environmental Monitoring. Advanced Sensor Research. 2024; 3(12): 2400066.
31. Rehrl J, Celikovic S, Castillo I, et al. A systematic modeling approach for continuous flow synthesis applicable to real-time process control. Chemical Engineering Research and Design. 2025; 216: 322–332.
32. Kourti T. Process analytical technology beyond real-time analyzers: The role of multivariate analysis. Critical Reviews in Analytical Chemistry. 2006; 36(3–4): 257–278.
33. Ündey C, Ertunç S, Mistretta T, et al. Applied advanced process analytics in biopharmaceutical manufacturing: Challenges and prospects in real-time monitoring and control. Journal of Process Control. 2010; 20(9): 1009–1018.
34. Svrcek WY, Mahoney DP, Young BR. A Real-Time Approach to Process Control. John Wiley & Sons; 2014.
35. Müller D, Dercks B, Nabati E, et al. Real-Time Optimization in the Chemical Processing Industry. Chemie Ingenieur Technik. 2017; 89(11): 1464–1470.
36. Sen M, Singh R, Ramachandran R. A hybrid MPC–PID control system design for the continuous purification and processing of active pharmaceutical ingredients. Processes. 2014; 2(2): 392–418.
37. Huang J, O'Connor T, Ahmed K, et al. AIChE PD2M advanced process control workshop-moving APC forward in the pharmaceutical industry. Journal of Advanced Manufacturing and Processing. 2021; 3(1): e10071.
38. Prakash J, Senthil R. Design of observer based nonlinear model predictive controller for a continuous stirred tank reactor. Journal of Process Control. 2008; 18(5): 504–514.
39. Qin SJ, Badgwell TA. A survey of industrial model predictive control technology. Control Engineering Practice. 2003; 11(7): 733–764.
40. Rawlings JB, Mayne DQ, Diehl MM. Model Predictive Control: Theory, Computation, and Design, 2nd ed. Nob Hill Pub; 2024.

41. D'Ambrosio B, Fehling MR, Forrest S, et al. Real-time process management for materials composition in chemical manufacturing. IEEE Intelligent Systems. 1987; 2(2): 80–93.
42. Lanzetti N, Lian YZ, Cortinovis A, et al. Recurrent neural network based MPC for process industries. In: Proceedings of the 2019 18th European Control Conference (ECC); 25–28 June 2019; Naples, Italy.
43. Kramer A, Morgado-Dias F. Applications of artificial neural networks in process control applications: A review. In: Proceedings of the 2018 International Conference on Biomedical Engineering and Applications (ICBEA); 9–12 July 2018; Funchal, Portugal.
44. Singh R, Sahay A, Karry KM, et al. Implementation of an advanced hybrid MPC–PID control system using PAT tools into a direct compaction continuous pharmaceutical tablet manufacturing pilot plant. International Journal of Pharmaceutics. 2014; 473(1–2): 38–54.
45. Fischer D, Sahre K, Abdelrhim M, et al. Process monitoring of polymers by in-line ATR–IR, NIR and Raman spectroscopy and ultrasonic measurements. Comptes Rendus Chimie. 2006; 9(11–12): 1419–1424.
46. Diehl M, Uslu I, Findeisen R, et al. Real-Time Optimization for Large Scale Processes: Nonlinear Model Predictive Control of a High Purity Distillation Column. In: Grötschel M, Krumke SO, Rambau J (editors). Online Optimization of Large Scale Systems. Springer; 2001. pp. 363–383.
47. Santos AF, Silva FM, Lenzi MK, et al. Monitoring and control of polymerization reactors using NIR spectroscopy. Polymer-Plastics Technology and Engineering. 2005; 44(1): 1–61.
48. Praveen M, Brogi S. Microbial fermentation in food and beverage industries: Innovations, challenges, and opportunities. Foods. 2025; 14(1): 114.
49. Zhao S, Jiao T, Adade SYSS, et al. Digital twin for predicting and controlling food fermentation: A case study of kombucha fermentation. Journal of Food Engineering. 2025; 393: 112467.
50. Vojinović V, Cabral J, Fonseca L. Real-time bioprocess monitoring: Part I: In situ sensors. Sensors and Actuators B: Chemical. 2006; 114(2): 1083–1091.
51. Raamets T, Karjust K, Hermaste A, et al. Planning and acquisition of real-time production data through the virtual factory in chemical industry. In: Proceedings of the ASME International Mechanical Engineering Congress and Exposition; 1–5 November 2021; Online.
52. Ambike A, Kim W, Kun J. Real-time operating environmentfor networked control systems. IEEE Transactions on Automation Science and Engineering. 2006; 3(3): 287–296.
53. Bhat S. Technology for Chemical Industry Mixing and Processing. Technology. 2015; 2(2).
54. Esmonde-White KA, Cuellar M, Lewis IR. The role of Raman spectroscopy in biopharmaceuticals from development to manufacturing. Analytical and Bioanalytical Chemistry. 2022; 414(2): 969–991.
55. Sommerfeld S, Strube J. Challenges in biotechnology production—Generic processes and process optimization for monoclonal antibodies. Chemical Engineering and Processing: Process Intensification. 2005; 44(10): 1123–1137.
56. Jagtap S, Rahimifard S, Duong LN. Real-time data collection to improve energy efficiency: A case study of food manufacturer. Journal of Food Processing and Preservation. 2022; 46(8): e14338.
57. Grassi S, Alamprese C. Advances in NIR spectroscopy applied to process analytical technology in food industries. Current Opinion in Food Science. 2018; 22: 17–21.
58. Cen H, He Y. Theory and application of near infrared reflectance spectroscopy in determination of food quality. Trends in Food Science & Technology. 2007; 18(2): 72–83.
59. Lavorato D, Piedepalumbo P. How smart technologies affect the decision-making and control system of food and beverage companies—A case study. Sustainability. 2023; 15(5): 4292.
60. Singh R, Velazquez C, Sahay A, et al. Advanced Control of Continuous Pharmaceutical Tablet Manufacturing Processes. In: Ierapetritou MG, Ramachandran R (editors). Process Simulation and Data Modeling in Solid Oral Drug Development and Manufacture. Springer; 2016. pp. 191–224.
61. Bakeev KA, Menezes JC. Future Trends for PAT for Increased Process Understanding and Growing Applications in Biomanufacturing. In: Bakeev KA (editor). Process Analytical Technology: Spectroscopic Tools and Implementation Strategies for the Chemical and Pharmaceutical Industries. John Wiley & Sons, Ltd.; 2010. pp. 521–543.
62. Chopda VR, Gomes J, Rathore AS. Bridging the gap between PAT concepts and implementation: An integrated software platform for fermentation. Biotechnology Journal. 2016; 11(1): 164–171.
63. Maruthamuthu MK, Rudge SR, Ardekani A, et al. Process Analytical Technologies and Data Analytics for the Manufacture of Monoclonal Antibodies. Trends in Biotechnology. 2020; 38(10): 1169–1186.
64. Pauli V, Roggo Y, Pellegatti L, et al. Process analytical technology for continuous manufacturing tableting processing: A case study. Journal of Pharmaceutical and Biomedical Analysis. 2019; 162: 101–111.

65. Müller DH, Flake C, Brands T, et al. Bioprocess in-line monitoring and control using Raman spectroscopy and Indirect Hard Modeling (IHM). Biotechnology and Bioengineering. 2024; 121(7): 2225–2233.
66. Sartori F. Effective Implementation of Industry 4.0 Approaches for Process Monitoring in the Batch Manufacturing of Specialty Chemicals [PhD thesis]. Università degli studi di Padova; 2024.
67. Claßen J, Aupert F, Reardon KF, et al. Spectroscopic sensors for in-line bioprocess monitoring in research and pharmaceutical industrial application. Analytical and Bioanalytical Chemistry. 2017; 409(3): 651–666.
68. Rathore AS, Nikita S, Jesubalan NG. Digitization in bioprocessing: The role of soft sensors in monitoring and control of downstream processing for production of biotherapeutic products. Biosensors and Bioelectronics: X. 2022; 12: 100263.
69. Sathiyapriyan P, Mukherjee S, Vogel T, et al. Current PAT Landscape in the Downstream Processing of Biopharmaceuticals. Analytical Science Advances. 2025; 6(1): e70013.
70. Wilson DM, Hoyt S, Janata J, et al. Chemical sensors for portable, handheld field instruments. IEEE Sensors Journal. 2001; 1(4): 256–274.
71. Frank R. Understanding Smart Sensors. Artech House; 2013.
72. Xu H, Yu W, Griffith D, et al. A survey on industrial Internet of Things: A cyber-physical systems perspective. IEEE Access. 2018; 6: 78238–78259.
73. Lea P. IoT and Edge Computing for Architects. Packt Publishing; 2020.
74. Mowbray M, Vallerio M, Perez-Galvan C, et al. Industrial data science—A review of machine learning applications for chemical and process industries. Reaction Chemistry & Engineering. 2022; 7(7): 1471–1509.
75. Butean A, Cutean I, Barbero R, et al. A review of artificial intelligence applications for biorefineries and bioprocessing: From data-driven processes to optimization strategies and real-time control. Processes. 2025; 13(8): 2544.
76. Friederich J, Francis DP, Lazarova-Molnar S, et al. A framework for data-driven digital twins of smart manufacturing systems. Computers in Industry. 2022; 136: 103586.
77. Pal PK, Hens A, Behera N, et al. Digital twins: Transforming the chemical process industry—A review. The Canadian Journal of Chemical Engineering. 2025; 103(8): 3611–3636.
78. Harries T, Hartnoll M, Hafezianrazavi M, et al. Digital twins for predictive maintenance. Procedia CIRP. 2023; 118: 306–311.
79. Jenck JF, Agterberg F, Droescher MJ. Products and processes for a sustainable chemical industry: A review of achievements and prospects. Green Chemistry. 2004; 6(11): 544–556.
80. UNEP. Assessing the Environmental Impacts of Consumption and Production: Priority Products and Materials—Summary. UNEP; 2010.
81. Rathore AS, Yu M, Yeboah S, et al. 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. 2008; 100(2): 306–316.