# A SYSTEMATIC REVIEW: EXPLORATION OF PROCESS ANALYTICAL TECHNOLOGY TECHNIQUES (PAT) AND THEIR MULTIFACETED ADVANTAGES IN INDUSTRIAL PROCESSES

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## ABSTRACT

FDA initiated the PAT technology framework in the year of 2004 with the guidelines of "A framework of innovative pharmaceutical development, manufacturing and quality assurance. With that, the International Council for Harmonisation has also initiated continuous process verification to overcome the limitations of traditional methods and improve the understanding of the process and quality of the product throughout the product lifecycle. Since the year of implementation, the advancement of analytical and chemometric tools has evolved to deliver consistent quality products by understanding their process and product performance. However, the pharmaceutical industry was lacking in this technicality and implementation of highly regulated specifications. To this respect, we have stated some of the PAT tools, including NIR, Raman and Terahertz spectroscopy, as they will transfer to the futuristic prospects of analyzing the drug product with non-destructive, improved process understanding, real-time monitoring, and enhanced data integrity. This review article emphasizes the importance of PAT technology with different monitoring processes with their historical background and regulatory framework. Special attention was given to strategies, challenges, opportunities, and the compatibility of PAT tools with data fusion. Further, this will give a high-priority disciplinary scientific topic to Pharma 4.0.

**Keywords:** PAT tools, NIR spectroscopy, Raman spectroscopy, Non-destructive, Real-time monitoring, Dissolution

## INTRODUCTION

In the Pharmaceutical industry, quality control was mainly based on end-product testing, a traditional approach based on a statistical process control approach [1]. The statistical method may include control charts, run charts, histograms, process capability analysis, or any other mathematical or statistical approaches; these are offline approaches, i.e., they focus only on the output of the process. All the offline processes are conducted to check the quality of the finished product. The main disadvantage of these traditional methods is that they mainly emphasize only the end product, and the root cause of the problem is unidentified or unclear [2-4]. Another drawback of this method is that it is very difficult to understand the process and solve the problems that arise during product manufacturing. The ICH (International Council for Harmonisation) initiated Continuous Process Verification (CVP) to overcome the limitations of traditional methods and improve the understanding of the process and quality of the product throughout the product lifecycle. It is the alternative technique for Statistical process control, which is an older approach. It enables to reduce the defects in the manufacturing process by continuous monitoring of the process. This gives a higher assurance of product quality [5].

In contrast, this approach is based upon scientific behavior and risk-based assessment to give a good quality finished product. In 2009, ICH laid down guideline Q8 (R2), which is a QbD approach that begins with a predefined objective. The main objective of this approach is a better understanding of the materials and the process parameters. It consists of six fundamental components that must be considered before the implementation of this approach. The framework consists of the following elements: defining the goal prior, identification of CQA (Critical Quality Attributes), Assessment of Risk, Design Space Development, Control Strategy, and Life Cycle Management [6-9].

Define the goal prior: It is the initial stage for the implementation of the QbD approach. Setting the goal before meeting the Target Specification is known as a Quality Target Product Profile (QTPP). It serves as a guideline for the development of quality products throughout the development stage and for the establishment of CQAs. Identification of CQAs: Evaluation of Quality Target Product Profile leads to the CQA development. It is directly proportional to the quality of the product. It is used in the risk assessment step to

check the root cause of the problem that arises during the product developmental stage. Assessment of Risk: It enables us to understand the factors that affect the quality of the product through root cause analysis. The factor may be CQA'S or any other process parameters. Design Space Development: It helps us to understand the combination and interaction effects of the parameters involved in the process. Identification of these enables an optimized process. Control Strategy: It is the ideas and information that is obtained from the previous manufacturing process, Literature survey, or any other process parameters. Life Cycle Management: It ensures that the product is maintained at good quality all the time by providing good manufacturing practices that ensure the product's quality throughout the life cycle. This may contain the following: Validation, Real-time monitoring, Six Sigma Approach, Training, etc [10].

In September 2004, the USFDA proposed "Guidance for Industry PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance," which is mainly focused on continuous process improvement and better understanding of the process. It also encourages the implementation of the Process Analytical Technique (PAT), which is an innovative approach. These guidelines are also the European Medical Agency and MHLW. Employing an analytical process with the PAT approach facilitates Real-time release testing (RTRT). There is an increasing use of PAT technologies, which are driven by innovative technologies that enable the improvement of the quality of the product. FDA consistently motivates the manufacturer to obey the Good Manufacturing Process, which QbD can implement, and PAT approaches. Understanding the process is made easy by using certain analytical tools, sensors, probes, and lasers that are placed in an appropriate position to provide a real-time monitoring facility. The data set obtained from those tools can be interpreted, and the real-time monitoring process is enhanced. These tools provide automation and optimization of the entire process, thus reducing the off-line testing of the products and thus reducing the time for analysis and fewer human errors [11-13].

In this review article, we have discussed the Guidelines released by the regulatory body USFDA that emphasize the implementation of the manufacturing process by means of any innovative real-time monitoring process that may include the PAT approach. We have also discussed the different monitoring processes, different PAT tools, and the analytical methods that are employed in the

monitoring of the process. The articles selected for the present review were systematically retrieved from several scholarly databases, such as Elsevier, PubMed, ScienceDirect, Google Scholar etc., in chronological order from 2001 to 2023. The search strategy included specific keywords such as PAT tools, NIR spectroscopy, Raman spectroscopy, Non-destructive, real-time monitoring, and dissolution, organized in chronological order to structure the review comprehensively.

**Different monitoring processes**

The process of manufacturing can be monitored by four methods (fig. 1): a) Off-line monitoring, b) At-line monitoring, c) In-line monitoring, and d) Online Monitoring.

Off-line Monitoring: In this monitoring process, the sample is taken from the ongoing manufacturing process and tested in a laboratory, and it is one of the traditional approaches involving repeated sampling and testing. It is a vigorous, lengthy process, time-consuming, transportation within the industry, and employment. At-line Monitoring: It is the process in which the samples are collected from the production batches and analyzed in the nearby location, and it is not directly integrated into the production line. By this, the

transportation from the production batch to the laboratory is decreased and provides more in-depth analysis than the online monitoring of the process. It consists of equipment that the manufacturing line can move. It has more robustness and sensitivity to the production environment and is not as precise as the offline testing of the samples. In-line Monitoring: It is a sampling-independent method where the samples are not collected from the production lines and thus provides real-time monitoring. This monitoring allows immediate or rapid feedback, allowing for rapid adjustments and corrections in the ongoing process. It is more effective in maintaining the quality of the products and compliance with the standard set of specifications from the regulatory agencies to meet the Good Manufacture Practice. It consists of sensors, mainly the optic sensors, which can precisely monitor the process parameters. These sensors are not hazardous to the production batches and can be placed in areas such as extreme temperature and pressure conditions. These are also made up of non-corrosive materials. On-line Monitoring: It involves continuously collecting the samples and analyzing the data in real-time through an automated system. It allows constant monitoring of the process and allows instant detection of deviations or problems in the production lines [14].
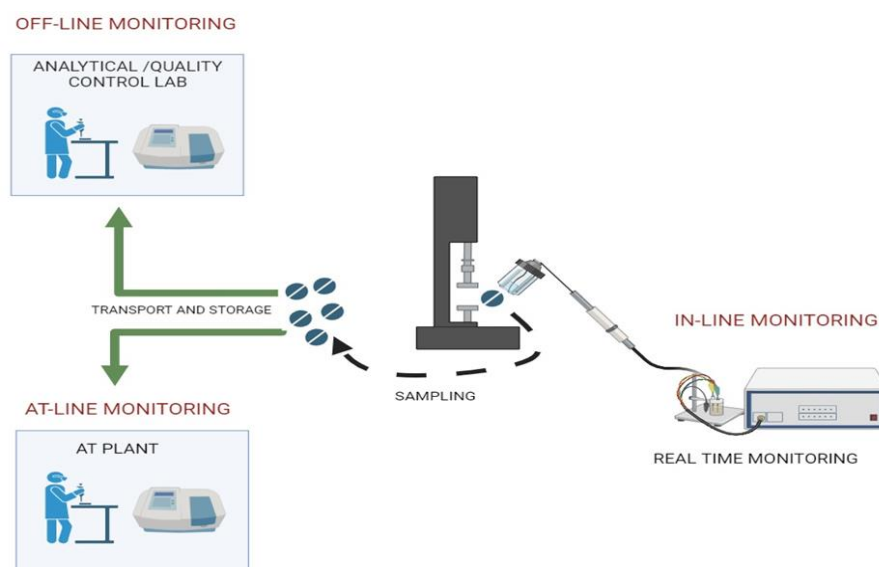


**Fig. 1: Different monitoring analysis of tablet compression [14]**

**Historical background and regulatory framework**

US FDA was the first to implement PAT, and later, it was adopted by ICH Q8. Now, these guidelines turn into "Science and Risk-based Guidelines" or QbD guidelines. PAT development has been recognized and supported by regulatory frameworks such as ICH Q8(R2) and Q11, both of which have adopted the concept and principles of PAT. ASTM, a worldwide recognized standard-setting organization, has formed a PAT community that has published pharmaceutical standard guidelines that specify terminology connected with Process Analytical Technology (PAT). Members of this group come from a variety of backgrounds, including industry, health agencies such as the FDA and EMA, and academia. In 2022, the FDA formed a subcommittee and assigned three tasks: Firstly, it was charged with describing the technology, explaining the regulatory hurdles, and offering viable solutions and methodologies for successful integration into pharmaceutical research and manufacturing processes. The committee's second objective was to deliberate on broad principles for the regulatory acceptance of PAT. This included addressing technique validation, establishing specifications, evaluating chemometric tools, and assessing the feasibility of applying parametric release. The third objective

involved the committee engaging in discussions about general PAT guidelines and putting them into practice. Before implementation, a supplementary application (CBE, CBE-30) could be presented to the agency. If deemed necessary, a team of investigators certified in PAT would conduct an inspection. Additionally, a comparability protocol outlining PAT research, validation, and implementation plans, along with associated timelines, could be submitted to the agency. Upon approval of this protocol, one or a combination of regulatory approaches could be chosen for execution [15].

**PAT tools**

There are several tools available to aid understanding of processes in scientific, risk-controlled pharmaceutical research, production, and quality assurance. When incorporated into a system, these technologies provide productive and simplified avenues for acquiring information, assisting with process comprehension, continuing improvement, and the development of risk-mitigation measures. These instruments are classed as follows under the Process Analytical Technology (PAT) framework: Multivariate tools (fig. 2), Process analyzers, Process controlling Tools, and Continuous improvement tools.
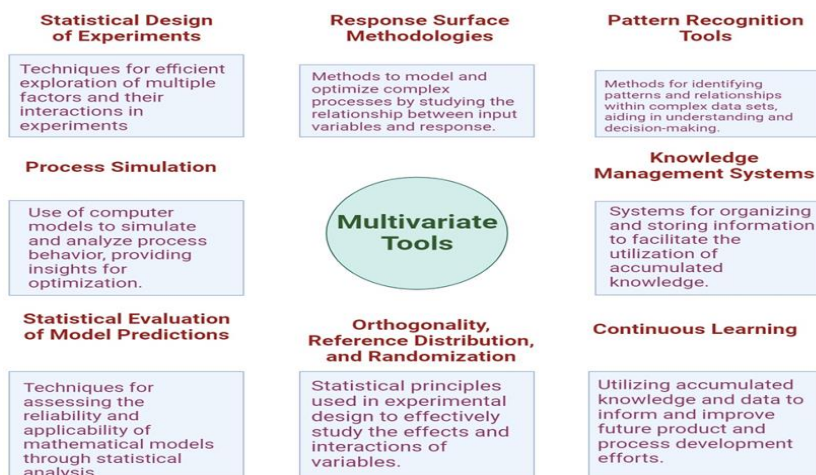
**Fig. 2: Multivariate tools [15]**

## Advantages and benefits of PAT

a) Improved process understanding: More information can be obtained from the ongoing process, and with the help of this information, the manufacturing process can be easily controlled and optimized. b) Real-Time Monitoring: By continuously monitoring the manufacturing process, the deviations from the process can be easily identified, and immediate necessary actions can be taken, thus providing a Six Sigma approach. c) Quality Assurance: By detecting the problems in real time, preventive and corrective actions can be implemented rapidly by enhancing the quality assurance process. d) By optimizing the process, wastes such as time, labor, and raw materials are eliminated during the manufacturing process, thus providing an efficient and effective manufacturing process. e) The product is manufactured in an accelerated and productive manner so that the pharmaceutical products reach the customer in a shorter period, thus avoiding scarcity of the product. Finally, the death rate may be decreased due to the availability of the drugs to the patients.

## Types of PAT techniques

### NIR spectroscopy

Near-infrared spectroscopy (NIRS) is a non-invasive technique for analyzing a wide range of substances. It includes wavelengths that are close to the mid-infrared spectrum and extend into the visible light range. Herschel is credited with finding the near-infrared area in 1800. He accomplished this feat by dispersing the electromagnetic spectrum with a prism and detecting a considerable rise in temperature beyond the red section, which we now call the near-infrared region. NIR experiments started at the beginning of the 1920s, but NIR spectroscopy did not find practical uses until the mid to end of the 1960s. Working with the United States Department of Agriculture, Karl Norris was essential in realizing the potential of this analytical approach, ushering in the contemporary era of NIR spectroscopy in industrial settings. Following this, significant progress was made in the method's advancement as a tool for industrial quality and process control, as seen by the implementation of effective chemometric data processing methods and the creation of new spectrometer configurations utilizing fiber optic probes. NIR spectroscopy has grown in popularity in the pharmaceutical industry for duties such as analyzing raw materials, assuring product quality, and monitoring processes. The pharmaceutical industry's increased interest in NIR spectroscopy is most likely due to its major benefits over alternative analytical methods. These benefits include its simple sample preparation, which eliminates the need for pretreatments, the ability to separate the sample measurement location from the spectrometer using fiber optic probes, and the ability to predict both the physical and chemical sample parameters from a single spectrum [16].

Accurate NIR spectra are heavily dependent on the sample's presentation, especially in the case of solid materials. This is critical because scatter effects and stray light, which might result from discrepancies in powder packing density or pill or capsule orientation, have the potential to introduce significant inaccuracies into the spectra. As a result of these problems, many types of sample containers have been developed. Quartz cuvettes with predefined optical path lengths for liquids, specialized sample cells with quartz windows for semi-solids and powders, and customized tablet and capsule holders are examples of these. Temperature control and sample motion management are two further characteristics that have been effectively implemented [17].

Certain aspects, such as light scattering, path length changes, and random noise, which are generated by fluctuating physical properties of the sample or instrumental impacts, necessitate mathematical modifications known as data pretreatments. Before doing multivariate modeling, these pretreatments are employed to minimize, eliminate, or standardize their influence on the spectra. Given that extensive data pretreatment can considerably increase a calibration model's reliability, we shall quickly explore the most commonly utilized procedures in terms of their corrective effects. Additional resources go into greater detail about these tactics [18].

Mathematical techniques are applied to compensate for baseline mismatches produced by scattering effects. Multiplicative Scatter Correction and Standard Normal Variation are two examples. Although both methods were developed to process reflectance spectra, they are also applicable to transmittance spectra. Normalization algorithms can reduce or eliminate baseline shifts and intensity fluctuations caused by varied sample locations or changes in path length. Derivatives can improve the resolution of overlapping spectral characteristics while also lowering baseline offsets. However, because derivatives can amplify spectral noise, they are frequently used in conjunction with smoothing methods such as Taylor or Savitzky Golay [19].

Before an NIR spectrometer can do quantitative analysis, it must go through a training process that includes multivariate calibration. In general, the calibration technique consists of the following stages. (1) Selecting a representative sample set of calibration samples, (2) Obtaining spectra and determining reference values, (3) Using multivariate modeling to establish the link between spectral variances and the analytical property of interest reference values, (4) Validating the model using approaches including cross-validation, set validation, and external validation [20]. The most often utilized multivariate regression procedures in quantitative NIR analysis are principal component regression and partial least squares regression.

Principal Component Regression (PCR) is a regression technique that uses the principal components produced from PCA to predict sample properties. Partial least squares (PLS) regression, on the other hand, identifies the axes, known as PLS components or PLS factors, that capture the most variability by considering both

spectral and target attribute information. The fundamental distinction between both of these techniques is how the first principal component or factor is interpreted: in PCR, it reflects the most significant changes in the spectrum, whereas, in PLS, it represents the most relevant variations with the strongest association with the target property values. In both cases, the optimal number of components used to generate the calibration model is determined by the sample properties and the analytical goal. Using an excessive number of components may result in an overfitted model with a high regression coefficient and a low standard error of calibration (SEC) but a considerable standard

error of prediction (SEP). This model is not robust and may fail when tested against an independent validation set [21].

Due to physical sample features or instrumental factors, the relationship between spectral data and the goal property may not always follow a linear pattern. Non-linear calibration techniques such as partial least squares-2, locally weighted regression, or artificial neural networks (ANNs) are employed to deal with such scenarios. Readers are recommended to check the relevant sections of a current multivariate calibration textbook for further in-depth information on these procedures [22].

**Table 1: List of In-line monitoring of parameters analyzed using NIR spectroscopy with the method of multivariate analysis**

| S. No. | Parameter analyzed | Multivariate analysis | Outcomes | References |
|---|---|---|---|---|
| 1 | Content of tablets and powders | Partial Least Square Regression | Laboratory-scale samples (40) were used for the calibration model. The error margins between unobserved laboratory powder samples and laboratory liquid powders vary from 0.4% to 5% for raw materials and 1.6% to 9% for tablets, indicating either model changes will be required. | [23] |
| 2 | Active pharmaceutical content in tablets | Partial Least Square Regression | The model had standard errors of prediction (SEP) of 0.1768 and 0.0682 mg, respectively. NIR predictions agreed closely with current methods for two low-dose pharmaceutical dosage forms, showing that diffuse reflectance NIR could emerge as a reliable quality control tool for consistently and robustly measuring the active content of the tablet. | [24] |
| 3 | Polymorphs characterization | Multivariate curve resolution | This approach discovered polymorphic Dexketoprofen Trometamol (DKP) transition in wet granulation samples but not in direct compaction samples. XRD and DSC were used to confirm the findings. Despite the fact that pure DKP was not present, the approach recognized amorphous and crystal forms. | [25] |
| 4 | Powder blending | Partial Least Square Regression | For in-line powder blending characterization, this study employs NIR spectroscopy. It creates a strong method for determining endpoints and assessing variability. Two different sensor positions were examined. The technique outperforms reference algorithms and advocates for the use of many sensors for accurate monitoring. | [26] |
| 5 | Analysis of the granulation process | Partial Least Square Regression, DoE | This work aimed to investigate the use of in-line NIR spectroscopy as a structure analysis tool for high-shear granulation. It used principal component analysis to analyze the three phases (mixing, sputtering, and wet mass) and collected key chemical and physical data. This includes consistency, liquid water content, and granular particle size. Special carriers corroborated their findings. In general, NIR spectroscopy provides a rapid in-line quality control tool for high-shear wet granulation. | [27] |
| 6 | Powder Blending | Partial Least Square Regression, PC-MBEST, SIMCA | This study emphasizes the importance of a comprehensive spectral database for successful NIRS application in powder blending control. It used experimental design to vary conditions and built models predicting blend homogeneity. Two algorithms, SIMCA and PC-MBEST, were evaluated and proved effective. | [28] |
| 7 | Moisture content in freeze-drying | Partial Least Square Regression | Multivariate NIR spectral analysis has shown the ability to predict the percentage of water in freeze-dried mannitol-sucrose mixtures, notably within moisture ranges up to about 5.5%. It is possible to develop multivariate NIR models for predicting water content, even with changing mannitol-sucrose ratios (1:9 to 9:1). The models closely reflect the reference method's inaccuracy. | [29] |

**Application of NIR spectroscopy in quality control**

To oversee operations and maintain product quality, NIRS assessments of particles have been performed in a variety of analysis modes (such as off-line, in-line, on-line, and at-line). NIRS can be used offline in the analytical lab after the process is completed or at-line near the production area to identify raw materials (such as API and excipients) and formulations using NIR spectroscopy [30]. Immediate measurements are also possible in online and in-line circumstances. Spectra from moving powder blends can be used to investigate processes such as hopper discharge. NIRS has been used to monitor a variety. When important attributes change, online and in-line analytics provide insights, allowing for continuous process management. These applications are described in detail in the following sections.

**Particle size**

Pharmaceutical particles are often an important quality factor affecting the flowability, mixability, and solubility of powders. Methods such as spectral pretreatment, including derivatives and

conventional normal transformations, cannot eliminate the effects of small-scale fluctuations. The link between particle size and NIR spectra, on the other hand, is complicated. Light-particle interaction has been studied for decades, and it continues to be a complex topic of study with different ideas attempting to explain the observed results [31, 32].

**Porosity and density**

Patient dosing can be closely monitored to control dosage and drug concentration in a formulation. NIRS has been investigated for its effectiveness in monitoring powder density, where the physical properties of materials influence the NIR spectrum. Nevertheless, accurate powder mass estimation remains a challenging task for NIRS. The main problem with developing a quantitative model for powder density is that its interpretation depends on the measurement conditions. This density test can be done by tapping or in an aerated powder after the powder has settled. The second challenge is to collect measurements that include expected changes in powder concentration during processing. However, several factors can contribute to the fluctuations in particle concentrations

during processing. Recent research has looked at three possible sources of such variability: 1. heterogeneity due to tap density, 2. variation resulting from application of different pressure levels, and 3. application of fixed force in compressibility tests using powder rheometers. Powder density changes are generally very small in many materials. However, a recent study confirmed the use of NIRS in a compound with significant density differences among the adjuvants used. Accurate density determination is also important in roller compaction; studies have been carried out to meet this need [33-36].

## Stability studies

The stability of chemicals and products is important to maintain safety and efficacy over the intended shelf life. Chemical stability studies are conducted to predict how a chemical or substance will change when subjected to various environmental factors such as temperature and humidity. These studies also provide information on material requirements for products that are about preservation. Chemical changes can be detected during stability tests. Polymorph changes, hydration-dehydration exchange, and deformation are all common processes that contribute to the instability of physical complexes [37].

## Crystallinity

Polymorphic modifications in the active component or some excipients are conceivable during the drying phase of wet granulation. This modification causes a dramatic change in crystalline hydrogen bonding in the case of glycine. Davis and colleagues have taken advantage of this to use NIRS to quantify polymorphic glycines during wet granulation successfully. Furthermore, the crystallization process can be followed at an earlier stage, specifically during active component manufacturing [38].

## Coating

Typically, the most important step in the final phase of pharmaceutical manufacturing is the application of coatings. It is important to ensure the quality and authenticity of this coating, as it can significantly influence aspects such as drug release and stability. This type of coating can be used in various coatings and formulations. Using fiber probing and NIR diffuse image spectrometry, the researchers were able to determine the thickness of film-coated pellets by partial least squares (PLS) model in some cases, such as Perez-Ramos *et al.* It appears that the investigation was established [39].

## Packaging

Drug packaging is the final step in pharmaceutical manufacturing, and a final analysis can also be performed in this final step. NIRS spectroscopy proved capable of thorough analysis of tablets during loading, up to 100% analysis. A principal component analysis (PCA) model was developed, which enabled the classification of up to 12,000 tablets per minute based on quality [40].

## Raman spectroscopy

Raman spectroscopy is a powerful observational technique that can be used to create a "molecular fingerprint" for a specific material. Being non-destructive, it can be used for chemical and molecular analysis. Raman spectroscopy has seen an increase in applications over the past 30 y in industries such as polymers, pharmaceuticals, bioprocesses, and biological research. Advances in laser technology and detectors have made Raman spectroscopy a useful tool in the laboratory and other places. It has been widely used for research drug development since the 1980s. Raman spectroscopy is capable of detecting and quantifying mixtures of multiple species in addition to distinguishing individual species from individual species. Raman has been used to analyze a wide range of systems since its initial discovery in lab applications in manufacturing, demonstrating its reliance on quantitative information. In-line Raman spectroscopy advantages, thus providing important system protection, allowing flexibility in configuration, assuring consistent production of desired APIs, Real-time testing releases, and support for streaming or streaming production [41, 42].

Raman spectroscopy works on the principle that monochromatic light interacts with molecular vibrations, phonons, or other excitations. When light hits a material, it changes energy, causing a change in frequency known as the Raman effect. This effect is slow, so it is necessary to use highly sensitive spectrometers to detect and analyze it, ultimately obtaining the necessary information. Raman spectroscopy is the most commonly used analytical method in Formulation development. This is due to the rapid determination of chemical composition and the composition of a wide range of samples such as solids, liquids, gases, gels, slurries and powders. It accomplishes this by providing detailed insights into their vibrational transitions. Unlike NIR spectroscopy, interpreting Raman data is very simple and does not always necessitate extensive multivariate modeling. Often, simple modeling of peak heights or ratios is sufficient to achieve the required results. It lends itself particularly well to incorporation into Process Analytical Technology (PAT) systems. This is due to the ability to work online or offline, allowing for accurate and consistent real-time inventory analysis at various stages of implementation. This provides both quantitative and qualitative information, and it significantly enhances project management and regulation. Raman spectroscopy is commonly used in the Formulation industry for the following purposes: Checking mixture uniformity, measuring active pharmaceutical ingredients (APIs) concentrations, Verifying the origin of raw materials, Impurities and contaminations that are detected and quantified [43, 44].

Recent advancements in Raman spectroscopy have greatly improved its adaptability and suitability for incorporation into continuous process monitoring systems such as Process Analytical Technology (PAT). These instruments have maintained a high level of accuracy and precision, making them suitable for use in highly regulated industries such as pharmaceutical manufacturing and pharmaceutical research. They immediately provide information on vital processes, allowing continuous monitoring of the system and routine implementation of improvement methods. It was used to do precise material studies, notably on liquids. Its data interpretation is often based on simple statistical models. However, because the Raman effect is so faint, detecting it requires expensive and extremely precise equipment. Impurity fluorescence and probable sample heating from laser light can both interfere with the Raman spectra. To mitigate these impacts, equipment must be thoroughly tuned and calibrated [45, 53].

**Table 2: List of In-line monitoring of parameters analyzed with the method of multivariate analysis using Raman spectroscopy**

| S. No. | Parameter analysed | Multivariate analysis | Outcomes | References |
|---|---|---|---|---|
| 1 | Active pharmaceutical ingredients in liquids | Partial Least Square Regression | The wide area illumination (WAI) Raman technique allowed for the successful non-destructive detection of povidone concentration in an eyewash solution via a plastic container, enhancing sample representation and repeatability and presenting possibilities for quality assurance in pharmaceutical manufacture. | [47] |
| 2 | Active pharmaceutical ingredient in suspensions | Partial Least Square Regression | The outcomes of this study confirm that the WAI method accurately measures the concentration of active medicinal ingredients in both transparent and cloudy solutions. | [48] |
| 3 | Tablets content uniformity | Partial Least Square Regression, PCA | With high confidence and few errors, our method can completely characterize a batch in as few tablets as 1083, making it suitable for online analysis. It surpasses the conventional test of only 30 tablets | [49] |

| S. No. | Parameter analysed | Multivariate analysis | Outcomes | References |
|---|---|---|---|---|
| | | | and allows a thorough batch quality assessment. The paper also proposes a promising wireless search method for large-scale tablets. | |
| 4 | Identification of counterfeit drugs | Principal component Analysis | Raman spectroscopy reliably distinguishes genuine antimalarial artesunate tablets from counterfeits and identifies counterfeits as well. The technology is compatible with other test methods and incorporates automated multivariate differential screening, emphasizing its potential to accelerate the approval of anti-malarial drugs. | [50] |
| 5 | Tablet identification | Partial Least Square Regression, | This paper provides a novel and quick Raman spectroscopy-based method for identifying pharmaceutical tablets, including the ability to distinguish between closely similar structures. Because it uses a calibration technique to determine the product group and formulation, the method is dependable. It has been validated and demonstrated to be beneficial for verifying release samples and detecting counterfeits. | [51] |
| 6 | The coating thickness of the tablet | Partial Least Square Regression, PCA | In this work, the Raman spectra of the chemical coatings are measured. Several methods were tested, and target factor analysis was found to work well, especially in the presence of TiO2. Fluorescence control enabled intensity-dependent measurements, and target factor analysis remained valid even when fluorescence levels varied. | [52] |

## CONCLUSION

Process Analytical Technology (PAT) has been used for the timely investigation of critical quality attributes that end up improving the final quality of the product with reduced manufacturing cost. It involves mostly real-time analysis to avoid the traditional destructive method. Additionally, it also promotes the continuous manufacturing of drug products with multivariate statistical analysis. The data was collected from the process parameter in which the patterns were recognized with the statistical tools of principle component analysis and partial least square. With this data acquisition, the final drug product performance can be predicted using multivariate analysis. Further, the physicochemical characteristics of the material, moisture absorption, content uniformity, particle size, polymorphism, stability studies, powder blending, granulation, and coating of the tablet can also be analyzed with spectral data. The insights of real-time monitoring will analyze all the parameter, which starts from initial blending to the final tablet compression. This non-destructive method of analysis will have a significant advance in investigating all the data mentioned above. The entire PAT framework, via the real-time monitoring analysis, will gain in-depth process understanding. If the PAT scientist establishes a well-defined state-art of implementing this approach, it will expect to inspire future trends in real-time monitoring. This will pave the way for the digital manufacturing process to declare a milestone for the fourth industrial revolution or Pharma 4.0.

## AUTHORS CONTRIBUTIONS

Raagul Seenivasan: Literature review, Data curation and Writing-original draft; Jey Kumar Pachiyappan: Literature review, Data curation and Writing-original draft, Conceptualization, Critical Evaluation; Murthannagari Vivek Reddy: Conceptualization; GNK Ganesh: Review and editing, Supervision, Evaluation, Visualization.

## CONFLICT OF INTERESTS

Declared none

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