JOURNAL OF PHARMA INSIGHTS AND RESEARCH ISSN NO. 3048-5428

REVIEW ARTICLE

Contemporary Trends in Analytical Spectroscopy and Integrating Qbd Principles for Enhanced Method Development

Mallika Adhatrao*

PG Scholar, Department Pharmaceutical Quality Assurance, DSTS Mandal's College of Pharmacy, Solapur, Maharashtra, India

Publication history: Received on 16th Aug; Revised on 27th Aug; Accepted on 1st September 2024

Article DOI: 10.69613/tne5y240

Abstract: Analytical spectroscopy has undergone significant advancements in recent years, driven by technological innovations and the demand for more robust, efficient, and reliable methods. The integration of Quality by Design (QbD) principles in spectroscopic method development has emerged as a powerful approach to enhance performance, reliability, and regulatory compliance. Contemporary trends in UV-Visible, Infrared (IR), Near-Infrared (NIR), Raman, Nuclear Magnetic Resonance (NMR), and Mass Spectrometry showcase remarkable progress in sensitivity, selectivity, and applicability. QbD implementation in method development, optimization, and validation has led to improved robustness and reduced method failures. Hyphenated techniques, coupling spectroscopy with separation methods, have expanded the analytical capabilities, enabling more comprehensive characterization of complex samples. Chemometrics and advanced data analysis techniques play a crucial role in extracting meaningful information from large spectral datasets. Regulatory agencies increasingly recognize the value of QbD in analytical methods, encouraging its adoption in the pharmaceutical and other regulated industries. Despite these advancements, challenges remain in standardizing QbD approaches and adapting to emerging technologies. Future directions point towards increased automation, miniaturization, and real-time monitoring capabilities in spectroscopic techniques.

Keywords: Analytical Spectroscopy; Quality by Design (QbD); Method Development; Chemometrics; Hyphenated Techniques.

1. Introduction

Quality by Design (QbD) is a systematic approach to development that has revolutionized the pharmaceutical industry and beyond, emphasizing product and process understanding based on sound science and quality risk management [1]. This concept, introduced by quality expert Joseph M. Juran, has been widely adopted by regulatory agencies, including the U.S. Food and Drug Administration (FDA) [2]. The International Conference on Harmonisation (ICH) Q8(R2) guideline on pharmaceutical development formally outlined QbD principles, providing a framework for its implementation [3].

At its core, QbD is built on several key principles that guide the development process. The first step involves defining the Target Product Profile, which identifies critical quality attributes (CQAs) essential for meeting user needs and ensuring product safety and efficacy [4]. This is followed by designing the product and process to consistently deliver the desired quality, a crucial step in maintaining product integrity [5]. Understanding the process is another fundamental aspect of QbD, which involves identifying critical process parameters (CPPs) and critical material attributes (CMAs) that significantly impact the CQAs [6]. This deep understanding allows for the establishment of a comprehensive control strategy to manage all aspects of the process that can affect product quality [7].

A key concept in QbD is the design space, defined as the multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality [8]. This concept provides flexibility in manufacturing while maintaining product quality [9].

Continual improvement is an integral part of QbD, emphasizing ongoing monitoring and enhancement of the process throughout the product lifecycle [10]. This principle as illustrated in Figure 1 ensures that the product and process evolve with technological advancements and changing regulatory requirements [11].

* Corresponding author: Mallika Adhatrao

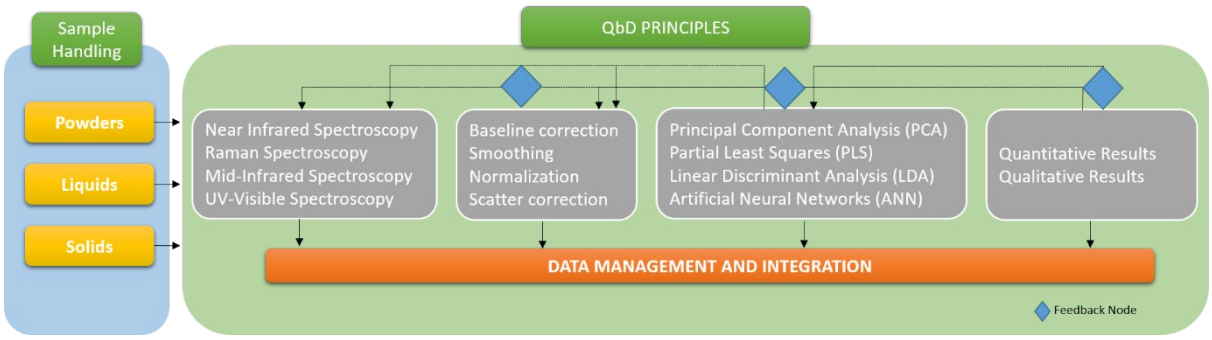

Figure 1. Applications of QbD principles to Analytical techniques

QbD employs various tools and methodologies to achieve its objectives. Risk assessment techniques, such as Failure Mode and Effects Analysis (FMEA), are used to identify and mitigate potential risks [12]. Design of Experiments (DoE) is utilized to efficiently explore the relationships between input variables and output responses [13]. Process Analytical Technology (PAT) provides real-time monitoring of critical quality attributes [14], while multivariate data analysis helps in interpreting complex datasets [15]. The implementation of QbD offers numerous benefits, including enhanced product quality and consistency, improved process understanding and control, and reduced risk of product failures [16]. It also provides greater regulatory flexibility and potential cost savings through reduced waste and improved efficiency [17].

QbD principles have found significant application in method development and optimization [18]. This involves defining an Analytical Target Profile (ATP), identifying Critical Method Parameters (CMPs) and Critical Method Attributes (CMAs), and establishing a Method Operable Design Region (MODR) [19]. These concepts, when applied to spectroscopic techniques, lead to more robust and reliable analytical methods [20].

Regulatory agencies have embraced QbD principles, recognizing their potential to enhance product quality and manufacturing efficiency [21]. The FDA's Process Validation Guidance and the ICH Q8, Q9, and Q10 guidelines provide a comprehensive framework for implementing QbD in pharmaceutical development and manufacturing [22]. While QbD offers numerous advantages, its implementation is not without challenges. It requires significant upfront investment in time and resources, necessitates a cultural shift towards proactive quality management, and demands advanced statistical and analytical skills [23]. However, these challenges are often outweighed by the long-term benefits of improved product quality and process efficiency [24]. As analytical spectroscopy continues to evolve, QbD principles are expected to play an increasingly important role in method development and optimization [25]. The integration of QbD with emerging technologies, such as artificial intelligence and machine learning, promises to further enhance the robustness, efficiency, and reliability of analytical techniques [26]. This synergy between QbD and advanced analytical methods is poised to drive innovation in pharmaceutical development and manufacturing, ultimately leading to higher quality products and more efficient processes [27]..

2. Integration of QbD in Spectroscopic Method Development

The integration of Quality by Design (QbD) principles into spectroscopic method development represents a significant advancement in analytical chemistry, offering a systematic approach to creating robust, reliable, and efficient analytical methods as shown in Table 1 [28]. This integration aligns spectroscopic techniques with regulatory expectations and enhances the overall quality of analytical results [29].

Table 1. QbD Implementation in Spectroscopic Method Development

QbD Element	Description	Benefits	Challenges in Implementation
Analytical Target Profile (ATP)	Defines method performance requirements based on intended use	Ensures method alignment with analytical needs, Facilitates regulatory compliance	Requires thorough understanding of method application, Balancing different stakeholder needs
Risk Assessment	Identifies and evaluates potential risks to method performance	Focuses development efforts on critical aspects, Enhances method robustness	Requires cross-functional expertise, Quantifying risk levels
Design of Experiments (DoE)	Systematic approach to explore method parameters and their interactions	Efficient optimization of method parameters, Reveals parameter interactions	Selecting appropriate experimental designs, Handling large number of factors

QbD Element	Description	Benefits	Challenges in Implementation
Method Operable Design Region (MODR)	Defines the range of method parameters where performance criteria are met	Provides flexibility in method operation, Facilitates method transfer	Requires extensive experimental work, Defining multidimensional spaces
Control Strategy	Defines how critical method parameters will be controlled during routine use	Ensures consistent method performance, Facilitates method lifecycle management	Implementing real-time monitoring systems, Balancing control and flexibility
Multivariate Data Analysis	Application of chemometric techniques for method development and validation	Extracts maximum information from spectral data, Improves method understanding	Requires specialized expertise, Ensuring model interpretability
Continuous Method Verification	Ongoing monitoring and improvement of method performance	Ensures sustained method performance, Facilitates continuous improvement	Implementing efficient data collection and analysis systems, Managing method changes
Knowledge Management	Systematic capture and utilization of knowledge gained during method development	Facilitates method troubleshooting and improvement, Supports organizational learning	Implementing effective knowledge management systems, Encouraging knowledge sharing

The first step in applying QbD to spectroscopic method development is defining the Analytical Target Profile (ATP) [30]. The ATP outlines the intended purpose of the method and specifies the required performance characteristics, including specificity, selectivity, limits of detection and quantification, precision, accuracy, linearity, and range [31]. For spectroscopic methods, additional considerations such as sample preparation requirements and analysis time constraints are also incorporated into the ATP. A thorough risk assessment follows, aimed at identifying potential factors that could impact method performance [32]. In spectroscopic methods, this might include instrument parameters (e.g., scan speed, resolution, detector sensitivity), sample-related factors (e.g., concentration, matrix effects, physical state), environmental conditions, and operator-dependent variables. Tools such as Ishikawa diagrams and Failure Mode and Effects Analysis (FMEA) are often employed in this stage to systematically evaluate and prioritize risks.

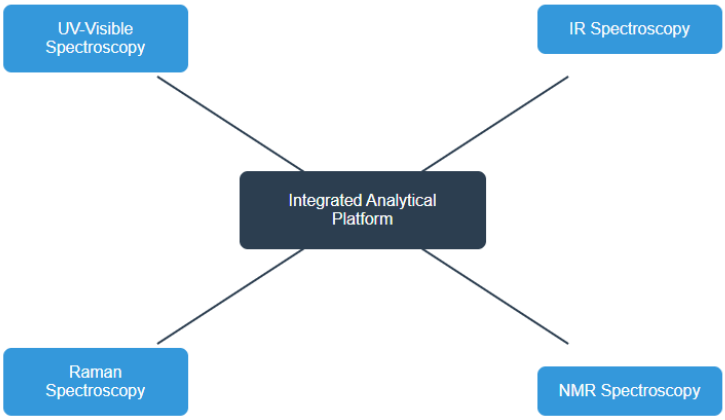

Figure 2. Integration of Modern Spectroscopic Techniques

Based on the risk assessment, Critical Method Parameters (CMPs) and Critical Method Attributes (CMAs) are identified [33]. These are the variables that have a significant impact on method performance. For spectroscopic methods, CMPs might include wavelength range, integration time, sample presentation, and data preprocessing techniques. CMAs could encompass spectral resolution, signal-to-noise ratio, and baseline stability. Design of Experiments (DoE) is a crucial tool in QbD-driven spectroscopic method development [34]. It allows for the systematic exploration of the effects of CMPs on method performance, optimization of instrument settings, determination of method robustness, and investigation of interactions between different parameters. The application of DoE in spectroscopic method development has led to more efficient optimization processes and a deeper understanding of method behavior. The Method Operable Design Region (MODR), analogous to the design space in product development, defines the range of method parameters within which the method consistently meets performance criteria [35]. For spectroscopic methods, this might be visualized as a multidimensional space of instrument and sample parameters. The MODR provides a clear understanding of the method's capabilities and limitations, allowing for more flexible and robust analytical procedures.

A control strategy is developed to ensure that the method remains within the MODR during routine use [36]. This typically includes regular system suitability tests, specified calibration procedures, defined sample preparation protocols, and data handling and processing guidelines. The control strategy is crucial for maintaining method performance over time and across different laboratories. QbD encourages ongoing monitoring of method performance and continuous improvement [37]. For spectroscopic methods, this might involve trending of system suitability results, periodic review of method performance against the ATP, and implementation of new technologies or data processing techniques as they become available. This continuous improvement approach ensures that the method remains state-of-the-art and continues to meet evolving regulatory and scientific standards.

Chemometric approaches play a significant role in QbD-driven spectroscopic method development [38]. Techniques such as Principal Component Analysis (PCA), Partial Least Squares (PLS) regression, and Multivariate Curve Resolution (MCR) are often employed for exploring data structure, quantitative analysis, and spectral deconvolution, respectively. These advanced data analysis techniques enhance the information extracted from spectral data and improve method performance. Method validation within the QbD framework focuses on demonstrating that the method performs as intended within the MODR [39]. This often involves robustness testing across the MODR, assessing method performance at the edges of the MODR, and demonstrating the predictive power of any chemometric models used. This comprehensive validation approach provides greater assurance of method reliability and applicability.

The integration of QbD principles into spectroscopic method development has led to several notable benefits [40]. These include improved method robustness and reliability, reduced method failures during routine use, greater flexibility in method parameters without compromising performance, and enhanced regulatory acceptance. Furthermore, the systematic approach of QbD has facilitated the transfer of spectroscopic methods between laboratories and the scaling up of analytical processes. As analytical technologies continue to advance, the role of QbD in spectroscopic method development is expected to grow. The integration of QbD with emerging technologies such as miniaturized spectrometers, hyphenated techniques, and artificial intelligence promises to further enhance the capabilities and reliability of spectroscopic methods [41].

2.1. Contemporary Trends in UV-Visible Spectroscopy

UV-Visible spectroscopy continues to evolve, driven by technological advancements and the increasing demand for more sensitive and versatile analytical methods [42]. Several contemporary trends are shaping the field:

2.1.1. Miniaturization:

The development of compact, portable UV-Visible spectrometers has expanded the application of this technique to on-site analysis in various fields, including environmental monitoring and point-of-care diagnostics [43].

2.1.2. Hyphenated techniques:

Combining UV-Visible spectroscopy with other analytical methods, such as HPLC-UV and LC-MS-UV, has enhanced the capabilities for complex mixture analysis [44].

2.1.3. Advanced detectors:

Photodiode array (PDA) and back-thinned CCD detectors have improved sensitivity and enabled simultaneous multi-wavelength detection, enhancing spectral analysis capabilities [45].

2.1.4. Chemometrics and data processing:

The application of multivariate analysis methods, such as partial least squares (PLS) regression and principal component analysis (PCA), has improved the extraction of information from complex spectra [46].

2.1.5. Artificial Intelligence and Machine Learning:

Integration of AI and ML algorithms with UV-Visible spectroscopy has opened new avenues for data analysis, method optimization, and predictive modeling [47].

2.1.6. Fiber-optic technology:

The development of fiber-optic UV-Visible spectroscopy has enabled real-time monitoring in challenging environments and industrial processes [48].

2.1.7. Time-resolved spectroscopy:

Advanced techniques like pump-probe spectroscopy have provided insights into ultrafast molecular dynamics and reaction kinetics [49].

2.1.8. Imaging spectroscopy:

The combination of spectral and spatial information has allowed for chemical composition mapping across sample surfaces [50].

2.1.9. Surface-enhanced spectroscopy:

Utilizing plasmonic nanostructures has pushed the boundaries of detection limits, enabling ultra-sensitive analysis in some cases [51].

2.1.10. Green analytical chemistry:

There is a growing emphasis on developing methods that minimize solvent use, reduce waste generation, and lower energy consumption. [52]

2.2. Advances in Infrared (IR) and Near-Infrared (NIR) Spectroscopy

IR and NIR spectroscopy have seen significant advancements in recent years, expanding their applications across various fields:

2.2.1. Fourier Transform IR (FTIR) improvements

Enhanced sensitivity and faster scanning capabilities have been achieved through advancements in interferometer design and detector technology [53].

2.2.2. Attenuated Total Reflection (ATR) accessories

The widespread adoption of ATR-FTIR has simplified sample preparation and enabled the analysis of a broader range of sample types, including liquids and semi-solids [54].

2.2.3. Quantum Cascade Lasers (QCLs)

The development of QCLs has led to more powerful, tunable IR sources, enabling new applications in gas sensing and imaging [55].

2.2.4. 2D correlation spectroscopy

This technique has improved the analysis of complex, overlapping spectral features and the study of dynamic systems [56].

2.2.5. Micro and nano-FTIR

The combination of FTIR with microscopy has allowed for high-resolution chemical imaging at the micro and nanoscale [57].

2.2.6. NIR imaging

Advancements in NIR imaging technology have expanded its use in pharmaceutical manufacturing, allowing for real-time monitoring of product quality and process control [58].

2.2.7. Multivariate calibration techniques

The development of advanced chemometric methods has improved the quantitative capabilities of NIR spectroscopy, particularly for complex mixture analysis [59].

2.2.8. Portable and handheld devices

Miniaturization of both IR and NIR spectrometers has enabled on-site analysis in fields such as agriculture, food quality control, and art conservation [60].

2.2.9. Hyperspectral imaging

The integration of spectral and spatial information has found applications in remote sensing, precision agriculture, and medical diagnostics [61].

2.2.10. Time-resolved IR spectroscopy

Ultrafast IR techniques have provided new insights into molecular dynamics and reaction mechanisms in chemistry and biology [62].

2.3. Innovations in Raman Spectroscopy

Raman spectroscopy has experienced significant advancements in recent years, expanding its applications across various fields:

2.3.1. Surface-Enhanced Raman Spectroscopy (SERS)

SERS has dramatically improved sensitivity, enabling single-molecule detection in some cases. Recent developments in nanostructured substrates and colloidal solutions have further enhanced SERS capabilities [63].

2.3.2. Tip-Enhanced Raman Spectroscopy (TERS)

TERS achieves nanoscale spatial resolution by combining Raman spectroscopy with scanning probe microscopy, opening new possibilities for surface analysis and materials characterization [64].

2.3.3. Coherent Anti-Stokes Raman Spectroscopy (CARS)

This nonlinear Raman technique offers improved sensitivity and faster acquisition times, finding applications in biomedical imaging and materials science [65].

2.3.4. Portable Raman spectrometers

Miniaturization has led to the development of handheld Raman devices, enabling on-site analysis in fields such as art conservation, forensics, and pharmaceutical quality control [66].

2.3.5. Time-resolved Raman spectroscopy

Advanced pulsed laser systems have enabled the study of fast chemical reactions and transient species, providing insights into reaction mechanisms and molecular dynamics [67].

2.3.6. Raman imaging and mapping

Improvements in detector technology and data processing have enhanced the spatial resolution and speed of Raman imaging, allowing for detailed chemical mapping of heterogeneous samples [68].

2.3.7. Multimodal Raman techniques

The combination of Raman spectroscopy with other analytical methods, such as AFM-Raman and Raman-SEM, has provided complementary information and expanded analytical capabilities [69].

2.4. Developments in Nuclear Magnetic Resonance (NMR) Spectroscopy

NMR spectroscopy continues to evolve, with recent developments enhancing its power and versatility:

2.4.1. Ultra-high field magnets

The development of magnets with field strengths exceeding 1 GHz has improved spectral resolution and sensitivity, enabling the study of more complex biomolecules and materials [70].

2.4.2. Cryogenic probes

These have significantly enhanced sensitivity, reducing experiment times and sample size requirements, particularly beneficial for biomolecular NMR studies [71].

2.4.3. Hyperpolarization techniques

Methods such as Dynamic Nuclear Polarization (DNP) and para-hydrogen induced polarization (PHIP) have dramatically increased signal intensity, enabling the study of low-concentration species and metabolic processes [72].

2.4.4. Benchtop NMR spectrometers

The development of compact, low-field NMR instruments has expanded the accessibility of NMR analysis, finding applications in quality control and education [73].

2.4.5. Fast acquisition techniques

Methods like non-uniform sampling (NUS) and single-scan 2D NMR have significantly reduced experiment times for multidimensional NMR experiments [74].

2.4.6. Solid-state NMR advancements

Improvements in magic-angle spinning (MAS) technology, including ultra-fast MAS probes, have expanded the capabilities of solid-state NMR for studying materials and large biomolecules [75].

2.4.7. In-cell NMR

This technique has enabled the study of biomolecules within their cellular environment, providing insights into protein structure and interactions under physiological conditions [76].

2.4.8. Diffusion-ordered spectroscopy (DOSY)

Advancements in DOSY have improved its ability to separate and characterize components in complex mixtures based on their diffusion coefficients [77].

2.4.9. Quantum computing in NMR

Emerging quantum technologies promise to enhance the sensitivity and information content of NMR experiments, potentially revolutionizing the field [78].

2.4.10. Metabolomics and chemical profiling

NMR has become a powerful tool in metabolomics studies, benefiting from improved spectral databases and advanced data analysis techniques [79].

2.5. Mass Spectrometry: Recent Progress and Applications

Mass spectrometry (MS) has undergone significant advancements in recent years, expanding its capabilities and applications across various scientific disciplines:

2.5.1. High-resolution mass spectrometry

The development of Orbitrap and Fourier Transform Ion Cyclotron Resonance (FT-ICR) instruments has dramatically improved mass accuracy and resolution, enabling more precise molecular characterization and formula determination [80].

2.5.2. Ion mobility spectrometry-mass spectrometry (IMS-MS)

This technique has enhanced the separation of complex mixtures and provided additional structural information based on molecular shape and size [81].

2.5.3. Ambient ionization techniques

Methods such as Desorption Electrospray Ionization (DESI) and Direct Analysis in Real Time (DART) have enabled rapid, direct analysis of samples with minimal preparation, finding applications in forensics, food safety, and pharmaceutical analysis [82].

2.5.4. Imaging mass spectrometry

Advancements in spatial resolution and speed have improved the capabilities of MS imaging, allowing for detailed molecular mapping of tissues and materials [83].

2.5.5. Single-cell mass spectrometry

This emerging technique enables the analysis of individual cells, providing insights into cellular heterogeneity and metabolomics at the single-cell level [84].

2.5.6. Top-down proteomics

Improvements in instrumentation and data analysis have enhanced the capabilities of analyzing intact proteins, providing more comprehensive characterization of proteoforms and post-translational modifications [85].

2.5.7. Data-independent acquisition (DIA)

This approach has improved the comprehensiveness and reproducibility of proteomics analyses, enabling more robust quantification and identification of proteins in complex samples [86].

2.5.8. Ion soft landing

This technique allows for the deposition of mass-selected ions onto surfaces, enabling the preparation of novel materials and the study of ion-surface interactions [87].

2.5.9. Miniaturized mass spectrometers

The development of portable MS instruments has expanded the possibilities for on-site analysis in environmental monitoring, space exploration, and clinical diagnostics [88].

2.5.10. Artificial intelligence in MS data analysis

Machine learning algorithms have enhanced the interpretation of complex MS data, improving compound identification and quantification in various applications [89].

Table 2. Comparison of Recent Advances in Major Spectroscopic Techniques

Technique	Key Advancements	Applications	Limitations
Near-Infrared (NIR) Spectroscopy	Miniaturization, Handheld devices, Improved detector sensitivity	Process monitoring, Pharmaceutical analysis, Food quality control	Limited sensitivity for minor components, Broad overlapping peaks
Raman Spectroscopy	Surface-enhanced Raman (SERS), Tip-enhanced Raman (TERS), Coherent anti-Stokes Raman (CARS)	Materials characterization, Biomedical imaging, Forensic analysis	Fluorescence interference, Sample heating, Limited quantitative capability
Fourier Transform Infrared (FTIR) Spectroscopy	Attenuated Total Reflection (ATR), Imaging FTIR, Quantum cascade lasers	Polymer analysis, Protein structure determination, Environmental monitoring	Water interference, Limited sensitivity for trace analysis
UV-Visible Spectroscopy	Multivariate curve resolution, Fiber optic probes, Microvolume analysis	Kinetics studies, Colorimetry, Quantitative analysis of mixtures	Limited structural information, Interference from sample turbidity
Nuclear Magnetic Resonance (NMR) Spectroscopy	Higher field strengths, Hyperpolarization techniques, Benchtop NMR	Structural elucidation, Metabolomics, Reaction monitoring	High cost, Low sensitivity, Complex data interpretation
Mass Spectrometry	High-resolution accurate mass, Ion mobility, Ambient ionization techniques	Proteomics, Metabolomics, Environmental analysis	Sample preparation requirements, Matrix effects, High cost
X-ray Spectroscopy	Synchrotron radiation sources, X-ray free-electron lasers, In-situ XAS	Materials science, Catalysis studies, Elemental speciation	Limited accessibility, Radiation hazards, Complex data analysis
Terahertz Spectroscopy	Improved sources and detectors, Time-domain systems, Imaging capabilities	Pharmaceutical polymorph analysis, Security screening, Semiconductor characterization	Limited penetration depth, Water absorption, Lack of spectral databases

3. Hyphenated Techniques: Coupling Spectroscopy with Separation Methods

Hyphenated techniques, which combine spectroscopic methods with separation techniques, have become increasingly important in analytical chemistry, offering enhanced selectivity and sensitivity:

- **Liquid chromatography-mass spectrometry (LC-MS):** Advancements in LC-MS interfaces, such as electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI), have improved the analysis of a wide range of compounds, from small molecules to large biomolecules [90].
- **Gas chromatography-mass spectrometry (GC-MS):** The development of comprehensive two-dimensional GC (GCxGC) coupled with high-resolution MS has enhanced the separation and identification of complex volatile mixtures [91].
- **Capillary electrophoresis-mass spectrometry (CE-MS):** Improvements in interfacing CE with MS have expanded its applications in proteomics, metabolomics, and the analysis of charged species [92].
- **Liquid chromatography-nuclear magnetic resonance (LC-NMR):** This technique combines the separation power of LC with the structural elucidation capabilities of NMR, providing detailed information on complex mixtures [93].
- **Ion mobility spectrometry-mass spectrometry (IMS-MS):** The coupling of IMS with MS has improved the separation and characterization of isomers and conformers in complex samples [94].
- **Liquid chromatography-infrared spectroscopy (LC-IR):** Advancements in flow cells and interfaces have enabled the combination of LC with IR spectroscopy, providing complementary structural information to MS detection [95].
- **Multidimensional separation techniques:** The development of two-dimensional liquid chromatography (2D-LC) and its coupling with MS has significantly enhanced the separation and analysis of extremely complex samples [96].
- **Supercritical fluid chromatography-mass spectrometry (SFC-MS):** This technique has gained importance in the analysis of non-polar and chiral compounds, offering advantages in terms of speed and selectivity [97].
- **Online solid-phase extraction-mass spectrometry (SPE-MS):** The automation and integration of sample preparation with MS analysis have improved throughput and sensitivity in various applications [98].
- **Thermal analysis-mass spectrometry (TA-MS):** The coupling of thermal analysis techniques (e.g., thermogravimetry) with MS has enhanced the characterization of materials and their thermal decomposition products [99].

4. Chemometrics and Data Analysis in Modern Spectroscopy

Chemometrics and advanced data analysis techniques have become integral to modern spectroscopy, enabling the extraction of meaningful information from complex spectral data:

- **Multivariate analysis:** Techniques such as Principal Component Analysis (PCA) and Partial Least Squares (PLS) regression have become essential tools for analyzing multidimensional spectral data, enabling pattern recognition, classification, and quantitative analysis [100].
- **Artificial Neural Networks (ANNs):** The application of ANNs in spectral data analysis has improved the modeling of non-linear relationships and enhanced predictive capabilities in various spectroscopic applications [101].
- **Support Vector Machines (SVMs):** SVMs have shown excellent performance in spectral classification tasks, particularly in cases with limited training data [102].
- **Genetic Algorithms (GAs):** GAs have been successfully applied to spectral feature selection and optimization of data preprocessing methods, improving model performance and interpretability [103].
- **Multiway analysis:** Techniques like PARAFAC (Parallel Factor Analysis) and Tucker decomposition have enabled the analysis of multi-dimensional spectral data, such as those obtained from hyperspectral imaging or time-resolved spectroscopy [104].
- **Bayesian methods:** The incorporation of Bayesian approaches in spectral data analysis has improved uncertainty estimation and enabled more robust parameter inference [105].
- **Transfer learning:** This approach has facilitated the adaptation of spectral models between different instruments or experimental conditions, enhancing the transferability of analytical methods [106].
- **Sparse methods:** Techniques like LASSO (Least Absolute Shrinkage and Selection Operator) have improved variable selection in spectral modeling, leading to more interpretable and robust models [107].
- **Deep learning:** Convolutional Neural Networks (CNNs) and other deep learning architectures have shown promise in spectral data analysis, particularly for image-based spectroscopic techniques [108].
- **Ensemble methods:** Techniques like Random Forests and Gradient Boosting have improved predictive performance and robustness in spectral classification and regression tasks [109].
- **Time series analysis:** Advanced time series analysis methods have enhanced the interpretation of dynamic spectral data, such as those obtained from reaction monitoring or process analytical technology (PAT) applications [110].
- **Fusion of spectral data:** Methods for combining data from multiple spectroscopic techniques have been developed, enabling more comprehensive characterization of complex samples [111].
- **Variable selection techniques:** Advanced algorithms for selecting the most informative spectral variables have improved model interpretability and reduced overfitting [112].

- **Outlier detection:** Robust methods for identifying and handling outliers in spectral data have enhanced the reliability of chemometric models [113].
- **Cloud-based data analysis:** The development of cloud-based platforms for spectral data analysis has facilitated collaborative research and enabled the processing of large-scale spectral datasets [114].

Table 3. Overview of Chemometric Methods in Spectroscopic Data Analysis

Method	Description	Advantages	Challenges	Common Applications
Principal Component Analysis (PCA)	Reduces data dimensionality by identifying principal components	Simplifies complex datasets, Reveals patterns and outliers	Interpretation of loadings, Handling non-linear relationships	Exploratory data analysis, Spectral preprocessing
Partial Least Squares (PLS) Regression	Builds predictive models relating spectral data to target variables	Handles multicollinearity, Efficient with high-dimensional data	Overfitting risk, Assumption of linearity	Quantitative analysis, Calibration transfer
Artificial Neural Networks (ANN)	Machine learning method inspired by biological neural networks	Can model complex non-linear relationships, Adaptable to various data types	Black-box nature, Requires large training datasets	Pattern recognition, Non-linear calibration
Support Vector Machines (SVM)	Classifies data by finding optimal hyperplanes in high-dimensional space	Effective for high-dimensional data, Robust to overfitting	Kernel selection, Computational intensity for large datasets	Classification, Anomaly detection
Multivariate Curve Resolution (MCR)	Decomposes mixed spectra into pure component spectra and concentrations	Resolves overlapping spectral features, Handles unknown components	Non-uniqueness of solutions, Convergence issues	Mixture analysis, Process monitoring
Independent Component Analysis (ICA)	Separates multivariate signals into independent source signals	Can separate statistically independent sources, Useful for blind source separation	Assumption of statistical independence, Scaling indeterminacy	Spectral unmixing, Artifact removal
Random Forests	Ensemble learning method using multiple decision trees	Handles non-linear relationships, Less prone to overfitting	Interpretation difficulty, Computationally intensive for large datasets	Classification, Feature importance ranking
Genetic Algorithms (GA)	Optimization method inspired by natural selection	Can optimize multiple parameters simultaneously, Handles complex search spaces	Computational intensity, Risk of premature convergence	Wavelength selection, Method optimization

5. QbD-driven Method Optimization and Validation

Quality by Design (QbD) principles have been increasingly applied to spectroscopic method development, optimization, and validation, leading to more robust and reliable analytical methods:

5.1.1. Analytical Target Profile (ATP)

The definition of ATPs for spectroscopic methods has improved the alignment of method performance with intended use and regulatory requirements [115].

5.1.2. Risk assessment

Systematic risk assessment techniques, such as Failure Mode and Effects Analysis (FMEA), have been applied to identify critical method parameters and potential sources of variability in spectroscopic methods [116].

5.1.3. Design of Experiments (DoE)

The application of DoE in spectroscopic method development has enabled efficient exploration of method parameters and their interactions, leading to optimized and robust methods [117].

5.1.4. Response surface methodology

This approach has been used to model the relationship between method parameters and performance characteristics, facilitating method optimization and understanding of parameter interactions [118].

5.1.5. Multivariate statistical process control

The implementation of multivariate control charts has improved the monitoring and control of spectroscopic methods during routine use [119].

5.1.6. Method operable design region (MODR)

The concept of MODR has been applied to spectroscopic methods, defining the multidimensional space within which the method consistently meets performance criteria [120].

5.1.7. Robustness testing

QbD approaches have enhanced robustness testing of spectroscopic methods, ensuring method performance across a range of operational conditions [121].

5.1.8. Analytical method lifecycle management

The application of QbD principles has facilitated a lifecycle approach to spectroscopic method development, validation, and continuous improvement [122].

5.1.9. Bayesian optimization

This approach has been used to efficiently optimize spectroscopic method parameters, particularly in cases with complex parameter interactions [123].

5.1.10. Process analytical technology (PAT)

QbD principles have been integrated with PAT applications of spectroscopic methods, improving process understanding and control in manufacturing [124].

5.1.11. Method transfer

QbD approaches have enhanced the transferability of spectroscopic methods between laboratories and instruments, ensuring consistent performance across different settings [125].

5.1.12. Uncertainty estimation

The incorporation of uncertainty estimation in method validation has improved the assessment of method reliability and fitness for purpose [126].

5.1.13. Multivariate method validation

Advanced approaches for validating multivariate spectroscopic methods have been developed, addressing the complexities of chemometric models [127].

5.1.14. Continuous method verification

QbD principles have facilitated the implementation of continuous method verification strategies, ensuring ongoing method performance and enabling timely method updates [128].

5.1.15. Knowledge management

Systematic approaches to capturing and utilizing knowledge gained during method development and validation have improved method understanding and facilitated continuous improvement [129].

6. Challenges

Despite significant advancements in spectroscopic techniques and data analysis, several challenges remain:

- **Big Data Management:** The increasing volume and complexity of spectral data, particularly from hyphenated and imaging techniques, pose challenges in data storage, processing, and interpretation [130].
- **Standardization and Harmonization:** Lack of standardized protocols for method development, validation, and data reporting across different industries and regulatory environments hinders method transferability and comparability [131].
- **Model Interpretability:** As machine learning models become more complex, ensuring interpretability and transparency in spectral data analysis becomes increasingly challenging [132].
- **Sample Matrix Effects:** Complex sample matrices can interfere with spectral measurements, requiring advanced techniques for matrix effect mitigation and robust calibration [133].
- **Non-linear Relationships:** Many spectroscopic applications involve non-linear relationships between spectra and analyte properties, necessitating sophisticated modeling approaches [134].
- **Method Transfer:** Transferring spectroscopic methods between different instruments or laboratories while maintaining method performance remains challenging [135].
- **Regulatory Acceptance:** Gaining regulatory acceptance for novel spectroscopic techniques and data analysis methods, particularly in highly regulated industries like pharmaceuticals, can be time-consuming and complex [136].
- **Miniaturization:** While progress has been made in developing portable spectroscopic instruments, maintaining high performance in miniaturized devices remains challenging [137].
- **Real-time Analysis:** Developing robust spectroscopic methods for real-time process monitoring and control, particularly in dynamic industrial environments, presents ongoing challenges [138].
- **Multivariate Calibration Maintenance:** Ensuring the long-term stability and reliability of multivariate calibration models for quantitative spectroscopic analysis remains challenging [139].
- **Integration of Multiple Data Sources:** Effectively combining data from different spectroscopic techniques and other analytical methods to gain comprehensive insights is an ongoing challenge [140].
- **Dealing with Heterogeneous Samples:** Developing spectroscopic methods capable of accurately analyzing heterogeneous samples, such as those encountered in biological and environmental applications, remains challenging [141].
- **Education and Training:** Keeping analysts and researchers up-to-date with rapidly evolving spectroscopic techniques and data analysis methods requires ongoing education and training efforts [142].
- **Cost and Accessibility:** High-end spectroscopic instruments and advanced data analysis software can be costly, limiting their accessibility, particularly in resource-constrained settings [143].
- **Automation and Artificial Intelligence:** While promising, the integration of automation and AI in spectroscopic analysis presents challenges in terms of validation, reliability, and user acceptance [144].
- **Spectral Interference:** Overlapping spectral features from different components in complex samples can complicate analysis and quantification [145].
- **Low Concentration Analysis:** Detecting and quantifying trace levels of analytes in complex matrices remains challenging for many spectroscopic techniques [146].
- **Data Security and Integrity:** Ensuring the security and integrity of spectral data, particularly in regulated environments or when using cloud-based solutions, is an ongoing concern [147].
- **Multidimensional Data Analysis:** Developing efficient algorithms for analyzing multidimensional spectral data, such as those from hyperspectral imaging or time-resolved spectroscopy, remains challenging [148].
- **Reference Material Availability:** The lack of suitable reference materials for calibration and validation of spectroscopic methods, especially for complex or novel analytes, can hinder method development [149].
- **In-situ and Remote Sensing:** Developing robust spectroscopic methods for in-situ or remote sensing applications, where sample preparation and measurement conditions cannot be tightly controlled, presents unique challenges [150].
- **Handling of Outliers:** Developing robust methods for identifying and handling outliers in spectral data, particularly in automated or high-throughput analysis, remains challenging [151].
- **Uncertainty Estimation:** Accurately estimating and reporting measurement uncertainty in complex spectroscopic analyses, especially those involving multivariate calibration, is an ongoing challenge [152].
- **Spectral Library Maintenance**: Keeping spectral libraries up-to-date and ensuring their applicability across different instruments and experimental conditions is challenging [153].

- **Instrument Drift and Aging:** Compensating for long-term instrument drift and aging effects in spectroscopic measurements, particularly in process analytical applications, requires ongoing attention [154].

7. Conclusion

The integration of Quality by Design principles and chemometric approaches has greatly enhanced the robustness and reliability of spectroscopic methods. While challenges remain, particularly in areas such as big data management, method transferability, and handling complex sample matrices, ongoing research and collaborative efforts continue to push the boundaries of what is possible with spectroscopic analysis. As these techniques evolve, they are poised to play an increasingly crucial role in fields ranging from pharmaceuticals and materials science to environmental monitoring and clinical diagnostics. The future of spectroscopy lies in the seamless integration of advanced instrumentation, sophisticated data analysis, and adaptive methodologies to address complex analytical challenges.

Compliance with ethical standards

Acknowledgements

Authors would like to thank Mr. Prakash Nathaniel Kumar Sarella, Aditya College of Pharmacy, Surampalem for his support to prepare this manuscript.

Conflict of interest statement

The authors declare that they have no competing interests or financial relationships that could have appeared to influence the work reported in this paper.

References

[1] Roggo Y, Chalus P, Maurer L, Lema-Martinez C, Edmond A, Jent N. A review of near infrared spectroscopy and chemometrics in pharmaceutical technologies. J Pharm Biomed Anal. 2007;44(3):683-700.

[2] Bakeev KA, editor. Process analytical technology: spectroscopic tools and implementation strategies for the chemical and pharmaceutical industries. John Wiley & Sons; 2010.

[3] Workman Jr J, Weyer L. Practical guide and spectral atlas for interpretive near-infrared spectroscopy. CRC press; 2007.

[4] Geladi P, Kowalski BR. Partial least-squares regression: a tutorial. Anal Chim Acta. 1986;185:1-17.

[5] Wold S, Sjöström M, Eriksson L. PLS-regression: a basic tool of chemometrics. Chemom Intell Lab Syst. 2001;58(2):109-30.

[6] Kudupudi V, Kakarparthy RS, Sarella PN, Kolapalli VR. Formulation Development and Characterization of Vancomycin Hydrochloride Colon-Targeted Tablets Using In-Situ Polyelectrolyte Complexation Technique. International Journal of Pharmaceutical Sciences and Nanotechnology (IJPSN). 2023 May 31;16(3):6533-45.

[7] Bocklitz T, Walter A, Hartmann K, Rösch P, Popp J. How to pre-process Raman spectra for reliable and stable models?. Anal Chim Acta. 2011;704(1-2):47-56.

[8] De Beer T, Burggraeve A, Fonteyne M, Saerens L, Remon JP, Vervaet C. Near infrared and Raman spectroscopy for the in-process monitoring of pharmaceutical production processes. Int J Pharm. 2011;417(1-2):32-47.

[9] Ravn C, Skibsted E, Bro R. Near-infrared chemical imaging (NIR-CI) on pharmaceutical solid dosage forms—comparing common calibration approaches. J Pharm Biomed Anal. 2008;48(3):554-61.

[10] Larkin P. Infrared and Raman spectroscopy; principles and spectral interpretation. Elsevier; 2011.

[11] Sarella PN, Godavari LR. The Expanding Scope of Emulgels: Formulation, Evaluation and Medical Uses. Int J Curr Sci Res Rev. 2023;6(5):3030-41.

[12] Siesler HW, Ozaki Y, Kawata S, Heise HM, editors. Near-infrared spectroscopy: principles, instruments, applications. John Wiley & Sons; 2008.

[13] Reich G. Near-infrared spectroscopy and imaging: basic principles and pharmaceutical applications. Adv Drug Deliv Rev. 2005;57(8):1109-43.

[14] Bro R. Multivariate calibration: What is in chemometrics for the analytical chemist?. Anal Chim Acta. 2003;500(1-2):185-94.

[15] Rinnan Å, Van Den Berg F, Engelsen SB. Review of the most common pre-processing techniques for near-infrared spectra. Trends Analyt Chem. 2009;28(10):1201-22.

[16] Gemperline P, editor. Practical guide to chemometrics. CRC press; 2006.

[17] Blanco M, Villarroya INIGO. NIR spectroscopy: a rapid-response analytical tool. Trends Analyt Chem. 2002;21(4):240-50.

[18] Arji SR, Eranki SS, Kadimi A, Sarella PN, Mangam VT. Development and validation of an HPLC method for the simultaneous estimation of salbutamol, theophylline and ambroxol in tablet dosage form. International Journal of Science and Research Archive. 2023;10(2):634-45.

[19] Bassbasi M, De Luca M, Ioele G, Oussama A, Ragno G. Prediction of the geographical origin of butters by partial least square discriminant analysis (PLS-DA) applied to infrared spectroscopy (FTIR) data. J Food Compost Anal. 2014;33(2):210-5.

[20] Jamrógiewicz M. Application of the near-infrared spectroscopy in the pharmaceutical technology. J Pharm Biomed Anal. 2012;66:1-10.

[21] Pasquini C. Near infrared spectroscopy: fundamentals, practical aspects and analytical applications. J Braz Chem Soc. 2003;14(2):198-219.

[22] Luypaert J, Massart DL, Vander Heyden Y. Near-infrared spectroscopy applications in pharmaceutical analysis. Talanta. 2007;72(3):865-83.

[23] Candolfi A, De Maesschalck R, Jouan-Rimbaud D, Hailey PA, Massart DL. The influence of data pre-processing in the pattern recognition of excipients near-infrared spectra. J Pharm Biomed Anal. 1999;21(1):115-32.

[24] Martens H, Næs T. Multivariate calibration. John Wiley & Sons; 1989.

[25] Barnes RJ, Dhanoa MS, Lister SJ. Standard normal variate transformation and de-trending of near-infrared diffuse reflectance spectra. Appl Spectrosc. 1989;43(5):772-7.

[26] Savitzky A, Golay MJ. Smoothing and differentiation of data by simplified least squares procedures. Anal Chem. 1964;36(8):1627-39.

[27] Storme-Paris I, Clarot I, Esposito S, Chaumeil JC, Nicolas A, Brion F. Near infrared spectroscopy homogeneity evaluation of complex powder blends in a small-scale pharmaceutical preformulation process, a real-life application. Eur J Pharm Biopharm. 2009;72(1):189-98.

[28] Mevik BH, Wehrens R. The pls package: principal component and partial least squares regression in R. J Stat Softw. 2007;18(2):1-24.

[29] Nicolaï BM, Beullens K, Bobelyn E, Peirs A, Saeys W, Theron KI, Lammertyn J. Nondestructive measurement of fruit and vegetable quality by means of NIR spectroscopy: A review. Postharvest Biol Technol. 2007;46(2):99-118.

[30] Gendrin C, Roggo Y, Collet C. Pharmaceutical applications of vibrational chemical imaging and chemometrics: A review. J Pharm Biomed Anal. 2008;48(3):533-53.

[31] Norris KH, Williams PC. Optimization of mathematical treatments of raw near-infrared signal in the measurement of protein in hard red spring wheat. I. Influence of particle size. Cereal Chem. 1984;61(2):158-65.

[32] Mangam VT, Sarella PN, Siddhantapu S, Sudhabattula S, Surampudi VA. Novel colorimetric approach for amikacin estimation in pure powder and its pharmaceutical formulations. World Journal of Biology Pharmacy and Health Sciences. 2023;14(1):270-9.

[33] Eriksson L, Johansson E, Kettaneh-Wold N, Trygg J, Wikström C, Wold S. Multi-and megavariate data analysis. Part I: basic principles and applications. Umetrics Inc.; 2006.

[34] Beebe KR, Pell RJ, Seasholtz MB. Chemometrics: a practical guide. New York: Wiley; 1998.

[35] Barker M, Rayens W. Partial least squares for discrimination. J Chemom. 2003;17(3):166-73.

[36] Cogdill RP, Drennen JK. Near-infrared spectroscopy in the pharmaceutical industry. Handbook of Vibrational Spectroscopy. 2006.

[37] Mangam VT, Narla D, Konda RK, Sarella PN. Beyond the spectrum: Exploring unconventional applications of fourier transform infrared (FTIR) spectroscopy. Asian Journal of Pharmaceutical Analysis. 2024;14(2):86-94.

[38] Trygg J, Wold S. Orthogonal projections to latent structures (O-PLS). J Chemom. 2002;16(3):119-28.

[39] Wold S, Antti H, Lindgren F, Öhman J. Orthogonal signal correction of near-infrared spectra. Chemom Intell Lab Syst. 1998;44(1-2):175-85.

[40] Fearn T. On orthogonal signal correction. Chemom Intell Lab Syst. 2000;50(1):47-52.

[41] Isaksson T, Næs T. The effect of multiplicative scatter correction (MSC) and linearity improvement in NIR spectroscopy. Appl Spectrosc. 1988;42(7):1273-84.

[42] Kennard RW, Stone LA. Computer aided design of experiments. Technometrics. 1969;11(1):137-48.

[43] Brereton RG. Chemometrics: data analysis for the laboratory and chemical plant. John Wiley & Sons; 2003.

[44] Daszykowski M, Walczak B, Massart DL. Representative subset selection. Anal Chim Acta. 2002;468(1):91-103.

[45] Blanco M, Coello J, Iturriaga H, Maspoch S, de la Pezuela C. Near-infrared spectroscopy in the pharmaceutical industry. Analyst. 1998;123(8):135R-150R.

[46] Burns DA, Ciurczak EW, editors. Handbook of near-infrared analysis. CRC press; 2007.

[47] Sarella PN, Vegi S, Vendi VK, Vipparthi AK, Valluri S. Exploring Aquasomes: A Promising Frontier in Nanotechnology-based Drug Delivery. Asian Journal of Pharmaceutical Research. 2024 May 28;14(2):153-61.

[48] Westerhuis JA, Hoefsloot HC, Smit S, Vis DJ, Smilde AK, van Velzen EJ, van Dorsten FA. Assessment of PLSDA cross validation. Metabolomics. 2008;4(1):81-9.

[49] Wold S, Ruhe A, Wold H, Dunn III WJ. The collinearity problem in linear regression. The partial least squares (PLS) approach to generalized inverses. SIAM J Sci Stat Comput. 1984;5(3):735-43.

[50] Olivieri AC. Introduction to multivariate calibration: a practical approach. Springer; 2018.

[51] Rinnan Å. Pre-processing in vibrational spectroscopy–when, why and how. Anal Methods. 2014;6(18):7124-9.

[52] Engel J, Gerretzen J, Szymańska E, Jansen JJ, Downey G, Blanchet L, Buydens LM. Breaking with trends in pre-processing?. Trends Analyt Chem. 2013;50:96-106.

[53] Næs T, Isaksson T, Kowalski B. Locally weighted regression and scatter correction for near-infrared reflectance data. Anal Chem. 1990;62(7):664-73.

[54] Feudale RN, Woody NA, Tan H, Myles AJ, Brown SD, Ferré J. Transfer of multivariate calibration models: a review. Chemom Intell Lab Syst. 2002;64(2):181-92.

[55] Rodionova OY, Houmøller LP, Pomerantsev AL, Geladi P, Burger J, Dorofeyev VL, Arzamastsev AP. NIR spectrometry for counterfeit drug detection: a feasibility study. Anal Chim Acta. 2005;549(1-2):151-8.

[56] Workman Jr JJ. Review of process and non-invasive near-infrared and infrared spectroscopy: 1993–1999. Appl Spectrosc Rev. 1999;34(1-2):1-89.

[57] Roggo Y, Jent N, Edmond A, Chalus P, Ulmschneider M. Characterizing process effects on pharmaceutical solid forms using near-infrared spectroscopy and infrared imaging. Eur J Pharm Biopharm. 2005;61(1-2):100-10.

[58] Haaland DM, Thomas EV. Partial least-squares methods for spectral analyses. 1. Relation to other quantitative calibration methods and the extraction of qualitative information. Anal chem. 1988;60(11):1193-202.

[59] Maesschalck RD, Jouan-Rimbaud D, Massart DL. The mahalanobis distance. Chemom Intell Lab Syst. 2000;50(1):1-18.

[60] Sarella PN, Vipparthi AK, Valluri S, Vegi S, Vendi VK. Nanorobotics: Pioneering Drug Delivery and Development in Pharmaceuticals. Research Journal of Pharmaceutical Dosage Forms and Technology. 2024 Feb 22;16(1):81-90.

[61] Shenk JS, Westerhaus MO. Population definition, sample selection, and calibration procedures for near infrared reflectance spectroscopy. Crop Sci. 1991;31(2):469-74.

[62] Goodacre R, Broadhurst D, Smilde AK, Kristal BS, Baker JD, Beger R, Wulfert F. Proposed minimum reporting standards for data analysis in metabolomics. Metabolomics. 2007;3(3):231-41.

[63] Næs T, Martens H. Principal component regression in NIR analysis: viewpoints, background details and selection of components. J Chemom. 1988;2(2):155-67.

[64] Wold S, Esbensen K, Geladi P. Principal component analysis. Chemom Intell Lab Syst. 1987;2(1-3):37-52.

[65] Rinnan Å, Andersson M, Ridder C, Engelsen SB. Recursive weighted partial least squares (rPLS): an efficient variable selection method using PLS. J Chemom. 2014;28(5):439-47.

[66] Norris K, Williams P. Optimization of mathematical treatments of raw near-infrared signal in the measurement of protein in hard red spring wheat. I. Influence of particle size. Cereal Chem. 1984;61(2):158-65.

[67] Zou H, Hastie T. Regularization and variable selection via the elastic net. J R Stat Soc Series B Stat Methodol. 2005;67(2):301-20.

[68] Tibshirani R. Regression shrinkage and selection via the lasso. J R Stat Soc Series B Methodol. 1996;58(1):267-88.

[69] Næs T, Mevik BH. Understanding the collinearity problem in regression and discriminant analysis. J Chemom. 2001;15(4):413-26.

[70] Westerhuis JA, Kourti T, MacGregor JF. Analysis of multiblock and hierarchical PCA and PLS models. J Chemom. 1998;12(5):301-21.

[71] Bro R, Smilde AK. Principal component analysis. Anal Methods. 2014;6(9):2812-31.

[72] De Jong S. SIMPLS: an alternative approach to partial least squares regression. Chemom Intell Lab Syst. 1993;18(3):251-63.

[73] Skov T, van den Berg F, Tomasi G, Bro R. Automated alignment of chromatographic data. J Chemom. 2006;20(11-12):484-97.

[74] Wise BM, Gallagher NB, Bro R, Shaver JM, Windig W, Koch RS. Chemometrics tutorial for PLS_Toolbox and Solo. Eigenvector Research, Inc. 2006;3905:102-59.

[75] Rajalahti T, Kvalheim OM. Multivariate data analysis in pharmaceutics: a tutorial review. Int J Pharm. 2011;417(1-2):280-90.

[76] Sarella PN, Valluri S, Vegi S, Vendi VK, Vipparthi AK. Microneedle Arrays: Advancements, Applications and Future Prospects in Pharmaceutical Delivery. Asian Journal of Pharmacy and Technology. 2024 Sep 19;14(3):229-36.

[77] Lorber A, Wangen LE, Kowalski BR. A theoretical foundation for the PLS algorithm. J Chemom. 1987;1(1):19-31.

[78] Wise BM, Gallagher NB. The process chemometrics approach to process monitoring and fault detection. J Process Contr. 1996;6(6):329-48.

[79] Ballabio D, Consonni V. Classification tools in chemistry. Part 1: linear models. PLS-DA. Anal Methods. 2013;5(16):3790-8.

[80] Sjöblom J, Svensson O, Josefson M, Kullberg H, Wold S. An evaluation of orthogonal signal correction applied to calibration transfer of near infrared spectra. Chemom Intell Lab Syst. 1998;44(1-2):229-44.

[81] Brereton RG, Lloyd GR. Partial least squares discriminant analysis: taking the magic away. J Chemom. 2014;28(4):213-25.

[82] Andersson CA, Bro R. The N-way toolbox for MATLAB. Chemom Intell Lab Syst. 2000;52(1):1-4.

[83] Geladi P, MacDougall D, Martens H. Linearization and scatter-correction for near-infrared reflectance spectra of meat. Appl Spectrosc. 1985;39(3):491-500.

[84] Kvalheim OM, Karstang TV. Interpretation of latent-variable regression models. Chemom Intell Lab Syst. 1989;7(1-2):39-51.

[85] Massart DL, Vandeginste BG, Deming SN, Michotte Y, Kaufman L. Chemometrics: a textbook (Vol. 2). Elsevier; 1988.

[86] Bro R. PARAFAC. Tutorial and applications. Chemom Intell lab syst. 1997;38(2):149-71.

[87] Wold S, Kettaneh N, Tjessem K. Hierarchical multiblock PLS and PC models for easier model interpretation and as an alternative to variable selection. J Chemom. 1996;10(5-6):463-82.

[88] Rodionova OY, Pomerantsev AL. Chemometrics: achievements and prospects. Russ Chem Rev. 2020;89(2):109-41.

[89] Næs T, Isaksson T, Fearn T, Davies T. A user-friendly guide to multivariate calibration and classification. NIR publications; 2004.

[90] Wold S, Kettaneh-Wold N, Skagerberg B. Nonlinear PLS modeling. Chemom Intell Lab Syst. 1989;7(1-2):53-65.

[91] Næs T, Martens H. Comparison of prediction methods for multicollinear data. Commun Stat Simul Comput. 1985;14(3):545-76.

[92] Smilde AK, Jansen JJ, Hoefsloot HC, Lamers RJANA, Van Der Greef J, Timmerman ME. ANOVA-simultaneous component analysis (ASCA): a new tool for analyzing designed metabolomics data. Bioinformatics. 2005;21(13):3043-8.

[93] Martens H, Naes T. Multivariate calibration. John Wiley & Sons; 1992.

[94] Næs T, Isaksson T, Kowalski B. Locally weighted regression and scatter correction for near-infrared reflectance data. Anal Chem. 1990;62(7):664-73.

[95] Bylesjo M, Rantalainen M, Cloarec O, Nicholson JK, Holmes E, Trygg J. OPLS discriminant analysis: combining the strengths of PLS-DA and SIMCA classification. J Chemom. 2006;20(8-10):341-51.

[96] Bro R, Smilde AK. Centering and scaling in component analysis. J Chemom. 2003;17(1):16-33.

[97] Westerhuis JA, Hoefsloot HC, Smit S, Vis DJ, Smilde AK, van Velzen EJ, van Dorsten FA. Assessment of PLSDA cross validation. Metabolomics. 2008;4(1):81-9.

[98] Wise BM, Gallagher NB, Bro R, Shaver JM, Windig W, Koch RS. PLS_Toolbox Version 4.0 for use with MATLAB™. Eigenvector Research, Inc. 2005;3905:102-59.

[99] Kvalheim OM. Interpretation of partial least squares regression models by means of target projection and selectivity ratio plots. J Chemom. 2010;24(7-8):496-504.

[100] Rajalahti T, Arneberg R, Berven FS, Myhr KM, Ulvik RJ, Kvalheim OM. Biomarker discovery in mass spectral profiles by means of selectivity ratio plot. Chemom Intell Lab Syst. 2009;95(1):35

[101] Tauler R, Maeder M, de Juan A. Multiset data analysis: extended multivariate curve resolution. In: Comprehensive chemometrics. Vol 2; 2009. p. 473-505.

[102] Jaumot J, Gargallo R, de Juan A, Tauler R. A graphical user-friendly interface for MCR-ALS: a new tool for multivariate curve resolution in MATLAB. Chemometr Intell Lab Syst. 2005;76(1):101-10.

[103] de Juan A, Tauler R. Multivariate curve resolution (MCR) from 2000: progress in concepts and applications. Crit Rev Anal Chem. 2006;36(3-4):163-76.

[104] Windig W, Guilment J. Interactive self-modeling mixture analysis. Anal Chem. 1991;63(14):1425-32.

[105] Eilers PH. Parametric time warping. Anal Chem. 2004;76(2):404-11.

[106] Trygg J, Lundstedt T. Chemometrics techniques for metabonomics. In: The handbook of metabonomics and metabolomics; 2007. p. 171-99.

[107] Brereton RG. Pattern recognition in chemometrics. Chemometr Intell Lab Syst. 2015;149:90-6.

[108] Arji SR, Eranki SS, Pecchetty S, Sarella PN. Unconventional stationary phases: Nanomaterials, nanoparticles and the future of liquid chromatography. World Journal of Advanced Research and Reviews. 2023;18(2):492-501.

[109] Wold S, Johansson E, Cocchi M. PLS: partial least squares projections to latent structures. In: 3D QSAR in drug design. Vol 1; 1993. p. 523-50.

[110] Kvalheim OM, Karstang TV. Interpretation of latent-variable regression models. Chemometr Intell Lab Syst. 1989;7(1-2):39-51.

[111] Bro R, Smilde AK. Principal component analysis. Anal Methods. 2014;6(9):2812-31.

[112] Ergon R. PLS post-processing by similarity transformation (PLS+ ST): a simple alternative to OPLS. J Chemometr. 2005;19(1):1-4.

[113] Skov T, Ballabio D, Bro R. Multiblock variance partitioning: A new approach for comparing variation in multiple data blocks. Anal Chim Acta. 2008;615(1):18-29.

[114] Indahl UG, Liland KH, Næs T. Canonical partial least squares—a unified PLS approach to classification and regression problems. J Chemometr. 2009;23(9):495-504.

[115] Kvalheim OM, Karstang TV. Interpretation of latent-variable regression models. Chemometr Intell Lab Syst. 1989;7(1-2):39-51.

[116] Martens H, Høy M, Wise BM, Bro R, Brockhoff PB. Pre-whitening of data by covariance-weighted pre-processing. J Chemometr. 2003;17(3):153-65.

[117] Wold S, Sjöström M, Eriksson L. PLS-regression: a basic tool of chemometrics. Chemometr Intell Lab Syst. 2001;58(2):109-30.

[118] Næs T, Martens H. Principal component regression in NIR analysis: viewpoints, background details and selection of components. J Chemometr. 1988;2(2):155-67.

[119] Smilde AK, Westerhuis JA, de Jong S. A framework for sequential multiblock component methods. J Chemometr. 2003;17(6):323-37.

[120] Wold S, Kettaneh N, Tjessem K. Hierarchical multiblock PLS and PC models for easier model interpretation and as an alternative to variable selection. J Chemometr. 1996;10(5-6):463-82.

[121] Verhulst A, Heyden YV, Remon JP, Massart DL. Method development strategy for the quantification of API in tablets by NIR spectroscopy. J Pharm Biomed Anal. 1997;15(7):895-907.

[122] Blanco M, Villarroya I. NIR spectroscopy: a rapid-response analytical tool. TrAC Trends Anal Chem. 2002;21(4):240-50.

[123] Cogdill RP, Drennen JK. Near-infrared spectroscopy. In: Spectroscopy of Pharmaceutical Solids; 2008. p. 313-412.

[124] Rinnan Å, Rinnan R. Application of near infrared reflectance (NIR) and fluorescence spectroscopy to analysis of microbiological and chemical properties of arctic soil. Soil Biol Biochem. 2007;39(7):1664-73.

[125] Burger J, Geladi P. Hyperspectral NIR image regression part I: calibration and correction. J Chemometr. 2006;20(5):193-201.

[126] Ozaki Y, McClure WF, Christy AA, editors. Near-infrared spectroscopy in food science and technology. John Wiley & Sons; 2006.

[127] Bakeev KA, editor. Process analytical technology: spectroscopic tools and implementation strategies for the chemical and pharmaceutical industries. John Wiley & Sons; 2010.

[128] Engel J, Gerretzen J, Szymańska E, Jansen JJ, Downey G, Blanchet L, et al. Breaking with trends in pre-processing?. TrAC Trends Anal Chem. 2013;50:96-106.

[129] Cozzolino D, Cynkar WU, Shah N, Smith P. Multivariate data analysis applied to spectroscopy: Potential application to juice and fruit quality. Food Res Int. 2011;44(7):1888-96.

[130] Savitzky A, Golay MJ. Smoothing and differentiation of data by simplified least squares procedures. Anal Chem. 1964;36(8):1627-39.

[131] Barnes RJ, Dhanoa MS, Lister SJ. Standard normal variate transformation and de-trending of near-infrared diffuse reflectance spectra. Appl Spectrosc. 1989;43(5):772-7.

[132] Rinnan Å, Van Den Berg F, Engelsen SB. Review of the most common pre-processing techniques for near-infrared spectra. TrAC Trends Anal Chem. 2009;28(10):1201-22.

[133] Westerhuis JA, Hoefsloot HC, Smit S, Vis DJ, Smilde AK, van Velzen EJ, et al. Assessment of PLSDA cross validation. Metabolomics. 2008;4(1):81-9.

[134] Næs T, Isaksson T, Fearn T, Davies T. A user-friendly guide to multivariate calibration and classification. NIR publications; 2002.

[135] Wold S, Sjöström M, Eriksson L. PLS-regression: a basic tool of chemometrics. Chemometr Intell Lab Syst. 2001;58(2):109-30.

[136] Geladi P, Kowalski BR. Partial least-squares regression: a tutorial. Anal Chim Acta. 1986;185:1-17.

[137] Kennard RW, Stone LA. Computer aided design of experiments. Technometrics. 1969;11(1):137-48.

[138] Shenk JS, Westerhaus MO. Population definition, sample selection, and calibration procedures for near infrared reflectance spectroscopy. Crop Sci. 1991;31(2):469-74.

[139] Mevik BH, Wehrens R. The pls package: principal component and partial least squares regression in R. J Stat Softw. 2007;18(2):1-24.

[140] Trygg J, Wold S. Orthogonal projections to latent structures (O-PLS). J Chemometr. 2002;16(3):119-28.

[141] Barker M, Rayens W. Partial least squares for discrimination. J Chemometr. 2003;17(3):166-73.

[142] Westerhuis JA, Kourti T, MacGregor JF. Analysis of multiblock and hierarchical PCA and PLS models. J Chemometr. 1998;12(5):301-21.

[143] Bro R, Smilde AK. Centering and scaling in component analysis. J Chemometr. 2003;17(1):16-33.

[144] Næs T, Martens H. Principal component regression in NIR analysis: viewpoints, background details and selection of components. J Chemometr. 1988;2(2):155-67.

[145] Wold S, Antti H, Lindgren F, Öhman J. Orthogonal signal correction of near-infrared spectra. Chemometr Intell Lab Syst. 1998;44(1-2):175-85.

[146] Beebe KR, Pell RJ, Seasholtz MB. Chemometrics: a practical guide. New York: Wiley; 1998.

[147] Rinnan Å, Andersson M, Ridder C, Engelsen SB. Recursive weighted partial least squares (rPLS): an efficient variable selection method using PLS. J Chemometr. 2014;28(5):439-47.

[148] Næs T, Mevik BH. Understanding the collinearity problem in regression and discriminant analysis. J Chemometr. 2001;15(4):413-26.

[149] Bro R. PARAFAC. Tutorial and applications. Chemometr Intell Lab Syst. 1997;38(2):149-71.

[150] Wise BM, Gallagher NB, Bro R, Shaver JM, Windig W, Koch RS. Chemometrics tutorial for PLS_Toolbox and Solo. Eigenvector Research, Inc; 2006.

[151] Rajalahti T, Kvalheim OM. Multivariate data analysis in pharmaceutics: a tutorial review. Int J Pharm. 2011;417(1-2):280-92.

[152] Trygg J, Wold S. O2-PLS, a two-block (X–Y) latent variable regression (LVR) method with an integral OSC filter. J Chemometr. 2003;17(1):53-64.

[153] Lorber A, Wangen LE, Kowalski BR. A theoretical foundation for the PLS algorithm. J Chemometr. 1987;1(1):19-31