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Applications of Raman and Near-Infrared Spectroscopy in Pharmaceutical Quality Control

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LIST OF ABBREVIATIONS

Abbreviation	Meaning
API	Active Pharmaceutical Ingredient
ATR	Attenuated Total Reflectance
CCD	Charge-Coupled Device
CMA	Critical Material Attribute
CPP	Critical Process Parameter
DoE	Design of Experiments
FDA	United States Food and Drug Administration
FT	Fourier Transform
GMP	Good Manufacturing Practice
HPLC	High-Performance Liquid Chromatography
ICH	International Council for Harmonisation
LFR	Low-Frequency Raman
NIR	Near-Infrared
NIRS	Near-Infrared Spectroscopy
PAT	Process Analytical Technology
PCA	Principal Component Analysis
PLS	Partial Least Squares
QbD	Quality by Design
QC	Quality Control
QRM	Quality Risk Management
RTT	Real-Time Testing
RTRT	Real-Time Release Testing
SEP	Standard Error of Prediction
SERS	Surface-Enhanced Raman Spectroscopy
SOP	Standard Operating Procedure
USP	United States Pharmacopeia

INTRODUCTION

The quality of a pharmaceutical product cannot be separated from the quality of the analytical information used to understand its materials and manufacturing process. A finished dosage form is expected to contain the correct active pharmaceutical ingredient (API), the intended amount of that API, appropriate excipients, acceptable physical characteristics, and adequate stability throughout its labelled shelf life. Conventional quality control has traditionally relied heavily on laboratory tests performed after a manufacturing step has been completed. Techniques such as chromatography, titrimetry, dissolution testing, Karl Fischer analysis and conventional spectroscopy remain essential, but they often involve sampling, transport, preparation, extraction or destruction of the sample. Modern pharmaceutical manufacturing increasingly seeks complementary analytical tools capable of generating information quickly and, where possible, directly from the process.

Raman and near-infrared spectroscopy occupy an important position in this context because both are vibrational spectroscopic methods and can interrogate materials with comparatively little sample preparation. Their usefulness extends beyond simple identification. With appropriate calibration and multivariate analysis, a spectrum can be related to concentration, moisture, physical attributes, solid-state characteristics and process conditions. Reviews of pharmaceutical NIR applications describe its use from raw-material identification to final-product assessment, while Raman and NIR have also been studied for in-process monitoring using fiber-optic probes and other process interfaces. [1–4]

The growing interest in these methods is closely connected with Process Analytical Technology (PAT), Quality by Design (QbD), continuous manufacturing and real-time release concepts. Rather than treating quality as something demonstrated only by testing the final batch, these approaches emphasize understanding how material attributes and process parameters influence critical quality attributes. Spectroscopic measurements can contribute to that understanding by producing frequent measurements during blending, granulation, drying, compression or coating. The information can then be interpreted using validated chemometric models and used to support process decisions.

The two techniques are not identical. Raman spectroscopy is based on inelastic scattering of monochromatic light and is particularly useful for molecular structures that produce strong changes in polarizability during vibration. NIR spectroscopy measures absorption in the near-infrared region and is strongly influenced by overtones and combination bands, particularly involving O–H, C–H and N–H groups. Consequently, Raman and NIR often respond differently to the same pharmaceutical matrix. This difference is analytically useful because the techniques can be selected according to the property of interest or used together for complementary information.

This thesis examines the applications of Raman and NIR spectroscopy specifically in pharmaceutical quality control. The objective is not simply to describe the theory of each technique, but to connect spectroscopic principles with practical pharmaceutical decisions. Particular attention is given to raw materials, finished dosage forms, process monitoring, chemometrics, validation, regulatory considerations, advantages, limitations and future developments.

Aim

To review the principles and applications of Raman and near-infrared spectroscopy as analytical tools for pharmaceutical quality control and process monitoring.

Objectives

- To explain the fundamental principles of Raman and NIR spectroscopy in relation to pharmaceutical analysis.
- To describe the major components and operating features of Raman and NIR instruments.
- To examine applications in identification and testing of pharmaceutical raw materials and finished dosage forms.
- To discuss the role of chemometric techniques in qualitative and quantitative pharmaceutical analysis.
- To evaluate applications within Process Analytical Technology and real-time release testing.
- To discuss method development, validation, sampling, calibration and regulatory considerations.
- To compare the analytical strengths and limitations of Raman and NIR spectroscopy.
- To identify emerging technologies and future opportunities for pharmaceutical quality control.

Scope of the Thesis

The thesis focuses on pharmaceutical materials and manufacturing operations, including APIs, excipients, powders, granules, tablets, capsules, coatings and selected liquid or semisolid systems. It considers laboratory, at-line, on-line and in-line applications where appropriate. The review emphasizes quality-related measurements rather than clinical diagnostic uses of Raman or NIR spectroscopy.

PHARMACEUTICAL QUALITY CONTROL AND THE NEED FOR RAPID SPECTROSCOPIC METHODS

Pharmaceutical quality control is a coordinated system of sampling, specification, testing, documentation and interpretation intended to establish whether materials and products meet predefined requirements. A quality control laboratory traditionally receives samples from manufacturing, performs validated procedures and compares the results with established specifications. This model remains indispensable, particularly when trace-level impurities, degradation products or complex mixtures must be separated and quantified. However, the increasing complexity of modern manufacturing has created demand for analytical methods that can provide information earlier in the process.

A major limitation of purely end-product testing is that a failing result may be obtained only after substantial material, time and processing resources have already been committed. If a process variable begins to drift during blending or drying, laboratory testing at the end of the operation may reveal the consequence but not necessarily the precise time at which the change occurred. Spectroscopic monitoring can reduce this information gap by providing repeated measurements during processing. NIR and Raman have therefore become relevant to PAT strategies, in which analytical measurements are integrated with process understanding and control.

Pharmaceutical samples also present analytical challenges. Tablets and powders can be heterogeneous, scattering can vary with particle size, moisture can influence physical properties, and excipients may overlap with API signals. A successful method must therefore address sampling as carefully as spectral measurement. NIR measurements are often strongly affected by physical factors such as particle size, density and path length, whereas Raman measurements may be affected by fluorescence, laser-induced heating or surface heterogeneity. Chemometric modelling is frequently required to distinguish chemical variation from physical or instrumental variation.

The economic and environmental dimensions are also relevant. Rapid spectroscopic measurements can reduce solvent consumption and, for suitable applications, eliminate destructive sample preparation.

Nondestructive analysis can allow a sample to be retained for further testing. Fiber-optic probes can place the measurement point close to the manufacturing operation, reducing the delay between the process and the analytical result. These benefits do not make spectroscopy automatically superior to chromatography or other established methods; rather, they provide a complementary route to faster and more information-rich quality assessment. [1,2]

For pharmaceutical quality control, the central question is therefore not whether Raman or NIR can produce a spectrum, but whether the complete analytical system—sampling, instrument, calibration model, reference method, software, operator and decision rule—can reliably answer a defined quality question. This systems perspective is essential when spectroscopic methods are used for routine release, process control or regulatory submissions.

Conventional Quality Control Versus Spectroscopic Quality Control

Feature	Conventional laboratory testing	Raman/NIR-based testing
Sampling	Usually requires physical sampling and laboratory transfer	Can be laboratory, at-line, on-line or in-line
Sample preparation	May require weighing, extraction, dilution or filtration	Often minimal; depends on matrix and method
Analysis time	Minutes to hours for many procedures	Often seconds to minutes for spectral acquisition
Sample consumption	Can be destructive	Frequently non-destructive
Data type	Often targeted analyte result	Full spectrum containing multicomponent information
Data interpretation	May rely on direct response or chromatographic separation	Often uses chemometrics and multivariate models
Process integration	Usually offline	Can be integrated with PAT systems
Main challenge	Time, preparation and laboratory workload	Calibration, sampling and model robustness

FUNDAMENTALS OF RAMAN SPECTROSCOPY

Raman spectroscopy is a vibrational spectroscopic technique in which a sample is irradiated with monochromatic light, usually from a laser, and the scattered radiation is measured. Most photons undergo elastic Rayleigh scattering and retain the energy of the incident light. A small fraction undergoes inelastic scattering, producing Raman-shifted photons whose energy differs from that of the incident radiation. The resulting Raman spectrum provides information related to molecular vibrations and chemical structure.

The Raman shift is commonly expressed in reciprocal centimetres (cm^{-1}). A vibrational mode is Raman-active when the vibration produces a change in the polarizability of the molecule. This selection rule differs from the absorption requirements governing infrared spectroscopy. As a result, Raman can be particularly informative for symmetric molecular vibrations and non-polar bonds that may be less prominent in conventional infrared absorption measurements.

In pharmaceutical analysis, Raman spectra can contain characteristic bands associated with APIs, excipients, polymorphic forms and other components. The position and relative intensity of these bands can support identification, while multivariate models can relate spectral patterns to concentration or physical attributes. Raman has an additional practical advantage for some aqueous systems because water often produces a

relatively weak Raman contribution compared with its strong absorption in parts of the infrared region. This property can be useful for selected aqueous formulations and process measurements.

A typical Raman measurement begins with laser illumination of the sample. The scattered light is collected by an optical system and passed through filters that reject the intense Rayleigh component. The remaining Raman signal is dispersed spectrally and detected, often using a charge-coupled device. Modern instruments may use different laser wavelengths, optical configurations and sampling accessories depending on the application. Longer-wavelength excitation can reduce fluorescence in some samples, although detector sensitivity and Raman scattering efficiency must also be considered.

Raman Instrumentation

- Laser source: supplies monochromatic excitation. Common excitation wavelengths include visible and near-infrared laser lines selected according to sample properties and fluorescence risk.
- Sampling optics: focus the laser on the sample and collect the scattered radiation. Fiber-optic probes allow measurements away from the main spectrometer.
- Rayleigh rejection filters: remove the intense elastically scattered light while transmitting Raman-shifted radiation.
- Spectrograph: separates scattered light according to wavelength or Raman shift.
- Detector: converts optical signal into an electronic spectrum. CCD-based detectors are widely used in many laboratory Raman systems.
- Software: performs acquisition, baseline correction, cosmic-ray removal, preprocessing, spectral matching and chemometric modelling.

Factors Affecting Raman Measurements

Fluorescence is one of the most important practical complications in Raman analysis. Some pharmaceutical ingredients, impurities, coatings, packaging materials or excipients can fluoresce under laser excitation, producing a broad background that may obscure weak Raman bands. Selection of a different excitation wavelength, mathematical baseline treatment, or specialized sampling approaches can sometimes reduce the problem. However, preprocessing should not be used to hide genuine analytical variability.

Laser power and exposure time must also be controlled. Excessive optical power may heat sensitive materials or cause photochemical changes. This is especially important for colored products, low-melting materials and samples containing photosensitive compounds. The sampling geometry, focus, particle size, surface roughness and orientation can affect the observed spectrum. For tablets, a measurement taken at one surface location may not represent the entire dosage unit when composition is heterogeneous.

Raman Modes Relevant to Pharmaceutical Analysis

Raman approach	Typical pharmaceutical value
Conventional backscattering Raman	Identification, raw-material verification, formulation characterization
Microscopic Raman	Spatially resolved analysis of particles, inclusions and formulation domains
Transmission Raman	Bulk analysis through intact tablets/capsules; useful for volumetric information
Low-frequency Raman	Investigation of lattice vibrations, crystallinity and solid-state differences
SERS	Enhanced detection of selected compounds using suitable enhancing substrates
Raman mapping/imaging	Distribution of API and excipients across a sample

Transmission Raman deserves particular attention in pharmaceutical quality control because it can provide volumetric information from intact dosage forms rather than relying only on a surface measurement. Literature has described its potential for quantitative bulk analysis of intact tablets and capsules, supporting quality and process control. [17] Low-frequency Raman has also attracted interest because low-wavenumber bands can provide information related to long-range order and crystallinity. [16]

FUNDAMENTALS OF NEAR-INFRARED SPECTROSCOPY

Near-infrared spectroscopy measures absorption of electromagnetic radiation in the near-infrared region, commonly approximately 780–2500 nm, although practical instrument ranges vary. Unlike mid-infrared spectroscopy, where fundamental molecular vibrations dominate, NIR spectra are mainly composed of overtone and combination bands. These bands are broader and often overlap extensively. Consequently, NIR spectra can be difficult to interpret by direct visual inspection but can contain substantial quantitative information when combined with multivariate calibration.

The most important NIR absorptions in pharmaceutical materials are commonly associated with O–H, C–H and N–H groups. Water is particularly influential because O–H absorptions are strong in the NIR region. This sensitivity makes NIR useful for moisture determination but also means that environmental humidity, sample temperature and packaging can affect measurements. NIR is also sensitive to physical characteristics such as particle size, density, scattering and packing.

NIR is widely recognized as a rapid, non-destructive technique with applications ranging from raw-material identification to process monitoring and finished-product quality assessment. Reviews have described its use for identification, water content, assay, physical properties, process monitoring and PAT. [1–3] More recent literature continues to describe applications in granulation, drying, tableting, coating, continuous manufacturing and real-time analysis. [6]

NIR Instrumentation

- Radiation source: provides broad-spectrum near-infrared illumination, often using tungsten-halogen or related sources in laboratory instruments.
- Optical system: directs radiation to and from the sample. Fiber optics may separate the measurement location from the spectrometer.
- Wavelength selector: dispersive or interferometric optical systems can be used to obtain spectral information.
- Detector: semiconductor detectors such as InGaAs or extended-range detectors are selected according to wavelength range.
- Reference system: background or reference measurements are used to convert raw detector responses into useful spectral quantities.
- Software and chemometrics: convert spectra into qualitative classifications or quantitative predictions.

Measurement Modes

NIR instruments can operate in reflectance, transmittance, transflectance and interactance arrangements. Reflectance measurements are convenient for powders, tablets and packaged products because the sample can often be measured directly from its surface. Transmittance is useful when radiation can pass through the sample sufficiently to obtain information from the bulk. The appropriate mode depends on sample thickness, optical properties, analyte concentration and the intended quality question.

Why NIR Is Useful for Pharmaceutical Materials

A major strength of NIR is the ability to obtain a spectrum from a sample without dissolving it. This is valuable for tablets and powders where destructive extraction would otherwise be required for some measurements. NIR can also be adapted to fiber-optic probes, allowing measurements in blenders, granulators, dryers and other equipment. The combination of rapid acquisition and multivariate analysis makes it suitable for frequent process measurements. However, the broad and overlapping nature of NIR bands means that calibration quality is central to method performance.

NIR methods are therefore developed around representative calibration sets rather than a single standard. Samples should span the expected variability in API concentration, excipient composition, moisture, particle size, manufacturing conditions and other relevant sources of variation. A model built from narrow or artificially uniform samples may perform well during development but fail when applied to routine production. Validation must therefore evaluate the intended operating range and the types of variability likely to occur in practice.

INSTRUMENTATION AND ANALYTICAL WORKFLOW

A spectroscopic method is more than an instrument and a spectrum. In pharmaceutical quality control, a defensible method includes the sample presentation system, measurement settings, spectral preprocessing, reference analytical procedure, calibration or classification model, validation strategy, software configuration, acceptance criteria and procedures for handling atypical spectra. The analytical workflow should be designed from the quality question backward.

General Workflow for Raman and NIR Quality Control

- Define the intended purpose and critical quality attribute.
- Select the spectroscopic technique and sampling configuration.
- Characterize expected material and process variability.
- Collect representative spectra and reference measurements.
- Perform appropriate spectral preprocessing.
- Develop qualitative or quantitative chemometric models.
- Evaluate independent validation samples.
- Establish system suitability and monitoring procedures.
- Define decision rules and out-of-model handling.
- Document the method and implement lifecycle monitoring.

Sampling Strategy

Sampling is often the most underestimated part of a spectroscopic method. A spectrum may be precise for the location measured while still being unrepresentative of the batch. Powders can segregate, tablets can show surface-to-core differences, and granules may have heterogeneous moisture distribution. For in-process applications, probe location, measurement frequency and sample movement must be considered. For laboratory applications, the number and location of measurements should reflect the intended inference.

Replicate spectra can help characterize measurement repeatability, but replication cannot substitute for representative sampling. If a blend contains segregation patterns, repeatedly measuring the same location

only demonstrates instrument repeatability. A more useful design measures multiple locations, times or sample portions that capture the expected variability.

Instrument Qualification and Routine Checks

Routine use requires confidence that the instrument is operating within its qualified performance. Checks may include wavelength or wavenumber accuracy, spectral response, signal-to-noise characteristics, reference material performance and software integrity, depending on the instrument and intended use. The exact qualification approach should be established according to the manufacturer's documentation, laboratory procedures and regulatory expectations.

Raman Versus NIR Measurement Environment

Consideration	Raman	NIR
Major spectral basis	Inelastic scattering	Absorption of NIR radiation
Common concern	Fluorescence	Scattering and environmental effects
Water influence	Often relatively manageable in aqueous matrices	Strong influence
Chemical selectivity	Often sharp, structurally informative bands	Broad, overlapping bands
Chemometrics	Useful, especially for complex formulations	Frequently essential for quantitative work
Fiber-optic process use	Well established for selected applications	Well established for many process applications
Surface/bulk sensitivity	Depends strongly on geometry; transmission can probe bulk	Depends strongly on measurement mode and optical path

CHEMOMETRICS AND DATA INTERPRETATION

Chemometrics is the mathematical and statistical discipline used to extract useful chemical information from multivariate measurements. It is central to NIR spectroscopy because individual NIR bands are broad and overlapping, and it is increasingly important in Raman analysis when formulation components, physical variability or weak signals complicate direct spectral interpretation. A chemometric model should be treated as part of the analytical method and therefore should be developed, validated, documented and maintained with the same scientific care as other analytical procedures.

Spectral Preprocessing

Raw spectra may contain baseline shifts, scattering effects, random noise, cosmic-ray spikes, path-length differences and other instrumental contributions. Common preprocessing approaches include baseline correction, smoothing, derivatives, normalization, multiplicative scatter correction and standard normal variate transformation. The choice should be based on a demonstrated analytical need. Excessive preprocessing can remove chemically meaningful information or create artificial structure.

Principal Component Analysis

Principal Component Analysis (PCA) is an unsupervised multivariate technique that reduces the dimensionality of spectral datasets while retaining major patterns of variance. In pharmaceutical spectroscopy, PCA can help visualize clusters associated with raw-material identity, formulation differences, polymorphic forms or process stages. It can also help identify unusual spectra that deserve investigation. PCA is primarily exploratory and should not automatically be interpreted as a validated quantitative method.

Partial Least Squares Regression

Partial Least Squares (PLS) regression is widely used to relate spectral variables to a reference concentration or physical property. The method compresses correlated spectral variables into latent factors selected to explain covariance between spectral data and the reference response. Model performance is evaluated using appropriate calibration and independent validation statistics. The number of latent variables should be justified rather than selected solely because it produces the smallest calibration error.

Classification Methods

Qualitative pharmaceutical identification may use spectral libraries, correlation methods, PCA-based classification or supervised algorithms. A useful identification model should be trained using authentic materials and should include relevant sources of variability. For raw-material identification, the model should distinguish the intended material from likely substitutes, related materials and common excipients where appropriate.

Model Validation

Model validation should address the intended use. For a quantitative method, relevant characteristics include accuracy, precision, range, specificity or selectivity, robustness and appropriate prediction performance. ICH Q2(R2) emphasizes that analytical procedures should be demonstrated to be suitable for their intended purpose and describes validation characteristics such as specificity/selectivity, accuracy and precision in appropriate contexts. [5] For spectroscopic methods, these concepts must be considered together with model applicability, representative calibration design and spectral domain coverage.

Chemometric stage	Key question
Data collection	Does the dataset represent expected material and process variability?
Preprocessing	Does the transformation improve relevant signal without distorting chemistry?
Model building	Is the model appropriately complex for the intended purpose?
Internal validation	Does the model perform consistently within development data?
External validation	Does it predict independent samples from the intended population?
Outlier assessment	Are unusual samples investigated rather than automatically deleted?
Lifecycle monitoring	Does model performance remain acceptable over time?

APPLICATIONS OF RAMAN SPECTROSCOPY IN PHARMACEUTICAL QUALITY CONTROL

Raman spectroscopy has developed from a primarily structural technique into a practical pharmaceutical analytical tool. Its ability to provide characteristic molecular fingerprints, its compatibility with fiber-optic sampling, and the availability of transmission and microscopic configurations have expanded its usefulness in quality control and process analysis. Raman applications range from simple identity testing to complex multivariate measurements of formulation composition and solid-state properties.

Identification of APIs and Excipients

One of the most direct uses of Raman spectroscopy is identity testing. A material produces a characteristic spectral pattern arising from its molecular structure. The spectrum can be compared with a qualified reference spectrum or library. In a pharmaceutical warehouse, portable or benchtop Raman instruments may be used to screen incoming containers with limited sample manipulation. This can support rapid verification of raw materials before they are released to manufacturing.

A practical identity method must account for packaging and measurement geometry. Some containers are Raman-active, some may fluoresce, and labels or liners can introduce spectral contributions. A library method should therefore be developed and verified using the actual measurement configuration. When packaging is intentionally included in the measurement, the model should be capable of distinguishing the material signal from packaging contributions.

Assay and Quantitative Analysis

Quantitative Raman analysis uses spectral intensity or multivariate spectral features to estimate the concentration of an API or other component. This approach is particularly useful when Raman bands of the target are sufficiently selective. For complex formulations, PLS regression or related multivariate models may be used. The model is calibrated against reference concentrations obtained by a validated laboratory procedure.

An important advantage of Raman quantitative analysis is the possibility of measuring intact dosage forms. Transmission Raman has been investigated for volumetric analysis of tablets and capsules, reducing dependence on surface sampling. [17] Such measurements may support rapid screening of assay and content uniformity, although the model must be validated for dosage-unit variability and manufacturing differences.

Content Uniformity and Blend Uniformity

Raman spectroscopy can be used to study the distribution of an API within a powder blend or dosage form. In a blending operation, repeated spectral measurements can reveal the point at which the spectral composition becomes sufficiently stable to support an endpoint decision. At the tablet level, Raman mapping can provide spatial information about the distribution of components.

Blend monitoring illustrates the difference between a laboratory spectrum and a process measurement. In a static sample, a spectrum represents a limited region. In a moving blender, the probe sees a continuously changing population of particles. Sampling frequency, probe location, blender geometry and particle segregation all affect the interpretation. A statistically stable spectral response may be more meaningful than a single absolute spectral value.

Polymorphism and Solid-State Characterization

Polymorphism can influence solubility, dissolution, stability and manufacturability. Raman spectra can distinguish solid forms because changes in crystal packing and molecular interactions can alter vibrational frequencies and band intensities. Raman microscopy and low-frequency Raman are particularly useful when subtle structural differences need to be investigated. Low-frequency Raman probes vibrational modes associated with long-range order and has therefore been studied for pharmaceutical solid-state analysis. [16]

Detection of Counterfeit or Substandard Medicines

Raman spectroscopy can provide rapid chemical fingerprints of finished medicines and has therefore been investigated for screening counterfeit or substandard products. The approach can compare a questioned dosage form with an authentic reference or classification model. The practical value lies in rapid triage: samples that differ substantially from the expected spectral pattern can be flagged for confirmatory laboratory testing.

Screening spectroscopy should not be confused with definitive regulatory determination unless the method has been validated for that purpose. Packaging, coatings, sample orientation and formulation variability can influence spectra. A robust screening system therefore requires representative authentic products and suitable controls.

Coating and Tablet Analysis

Raman measurements can be applied to tablets before and after coating to investigate formulation composition or coating-related changes. Depending on the optical configuration, information may be obtained from the surface or deeper regions. Spectral monitoring can support investigation of coating uniformity and formulation identity, while multivariate models can potentially estimate selected attributes.

Dissolution-Related Applications

Raman spectroscopy has been investigated as a complementary tool for studying dissolution and drug release. Because dissolution involves changes in concentration, solid state and molecular environment, spectral measurements can provide time-resolved information under suitable experimental conditions. The technique may therefore support mechanistic understanding, although conventional dissolution testing remains an established quality requirement and Raman-based alternatives require appropriate validation.

Injectable and Aqueous Formulations

Raman spectroscopy can be attractive for selected aqueous systems because water is a comparatively weak Raman scatterer relative to its strong infrared absorption. This makes it possible to investigate some aqueous pharmaceutical systems without the same degree of interference encountered in NIR. However, fluorescence, low analyte concentration, container effects and laser exposure must be considered. Literature on PAT for injectable products identifies both NIR and Raman as promising tools while also noting practical implementation challenges. [13]

Raman Imaging and Microscopy

Raman imaging combines spectral information with spatial information. In pharmaceutical research and quality control, it can reveal where an API or excipient is located within a formulation. Such information can help investigate segregation, coating structure, particle distribution and interactions between components. The principal limitation is that imaging can require substantially more acquisition time and data processing than a single-point spectrum.

Raman Application Summary

Application	Information obtained	Potential QC value
Raw-material ID	Molecular fingerprint	Rapid material verification
API assay	Spectral-to-concentration relationship	Quantitative testing
Blend monitoring	Composition changes over time	Blend endpoint/process control
Content uniformity	Unit-to-unit spectral variation	Screening and process understanding
Polymorph identification	Solid-state spectral differences	Form control
Tablet/capsule analysis	Surface or bulk composition	Non-destructive assessment
Counterfeit screening	Spectral similarity/difference	Rapid triage
Raman imaging	Chemical distribution	Investigation of heterogeneity

APPLICATIONS OF NEAR-INFRARED SPECTROSCOPY IN PHARMACEUTICAL QUALITY CONTROL

NIR spectroscopy has become an important pharmaceutical analytical technology because it can measure many materials rapidly without conventional wet-chemical sample preparation. Its applications extend from incoming raw materials to finished products and manufacturing processes. The technique is particularly valuable when a quality attribute can be correlated reliably with spectral variation through a validated multivariate model.

Raw-Material Identification

NIR can be used to identify APIs and excipients by comparing measured spectra with validated reference libraries or classification models. Because spectra can be collected through certain transparent packaging materials, NIR can sometimes reduce the need to open containers for preliminary identity verification. The actual suitability depends on the packaging material, analyte, optical configuration and validated measurement procedure.

A strong raw-material identification model should contain multiple lots and expected sources of variability. Differences caused by particle size, moisture, supplier, grade and packing should be represented when they are expected during routine use. The method should also define how uncertain or out-of-library spectra are handled.

Moisture Determination

Moisture is one of the most established pharmaceutical applications of NIR because water has strong and recognizable NIR absorption features. NIR can be used to estimate moisture in powders, granules and selected finished products when calibrated against an appropriate reference procedure. Rapid moisture monitoring can be especially useful during drying, where the objective is to determine when a process has reached an acceptable endpoint.

The relationship between spectral response and moisture may also depend on the physical state of the material. Bound and free water can contribute differently, and temperature may influence spectral features. Consequently, a calibration developed under one manufacturing condition should not automatically be assumed to be valid under another.

Assay of Pharmaceutical Dosage Forms

NIR can estimate API content in tablets, capsules and powders when spectral differences associated with concentration are measurable. PLS regression is commonly used for quantitative models. A validated model can potentially measure intact tablets without extraction, providing rapid information for screening or process control. The method should account for tablet hardness, weight, thickness, excipient variability and other factors that may affect the spectrum.

Content Uniformity

Because NIR acquisition can be rapid, many dosage units can be measured in a relatively short period. This makes it possible to investigate unit-to-unit variability and identify process changes. However, the spectral model must distinguish concentration effects from physical effects. A model that predicts tablet weight rather than API concentration, for example, may appear statistically successful but fail to answer the intended quality question.

Granulation Monitoring

During wet granulation, material moisture and physical structure change over time. NIR probes can be positioned to monitor spectral changes continuously. The resulting data can be correlated with process stages or reference moisture measurements. This can help identify a granulation endpoint based on material condition rather than a fixed processing time.

Drying Endpoint Determination

Drying is a critical operation because excessive moisture may compromise stability or flow, while excessive drying can also alter material properties. NIR can provide frequent moisture estimates during drying, allowing

the process trajectory to be followed. The approach can reduce dependence on intermittent sampling and laboratory moisture tests, provided the model is representative of the process.

Blend Uniformity

NIR is widely studied for blend monitoring because spectra can be collected rapidly and probes can be installed directly in mixing equipment. A time series of spectra can show the evolution from initial component segregation toward a more stable mixed state. Chemometric or spectral variability metrics may be used to support endpoint determination.

The definition of a blending endpoint should be scientifically justified. The objective is not necessarily to find the point at which spectra become mathematically identical, because real pharmaceutical blends retain natural variation. Instead, the process decision should be linked to the quality attribute and the acceptable variability established during development.

Tablet Compression Monitoring

NIR can be integrated with tablet presses or used at-line to investigate tablet composition and physical attributes. Variables such as compression force, tablet density and hardness can influence spectral response. Models may therefore be developed to estimate selected attributes or to detect process drift. This application demonstrates the importance of distinguishing chemical information from physical correlations.

Coating Monitoring

During film coating, NIR can monitor changes in the tablet surface and coating composition. Time-resolved spectral measurements can help identify coating progression and endpoint. The method can be particularly useful when the coating process is long and conventional sampling would require stopping or interrupting production.

Identification and Characterization of Counterfeit Products

NIR has been investigated as a rapid screening tool for distinguishing authentic products from suspicious products. Multivariate classification can capture spectral differences associated with API content, excipient composition, manufacturing variation and physical structure. As with Raman, screening results should be interpreted according to the validated intended purpose and confirmed using appropriate reference methods when necessary.

Continuous Manufacturing

Continuous pharmaceutical manufacturing creates a strong need for frequent process measurements. NIR probes can provide near-real-time information at multiple locations, including blending, granulation, drying and tablet production. When linked with control strategies, these measurements can support material tracking and process decisions. Recent reviews continue to identify NIR as an important tool for continuous manufacturing and real-time analysis. [6]

NIR Imaging

NIR imaging adds spatial information to spectral analysis. It can reveal distribution of components across pharmaceutical samples and may be useful for investigating coating layers, particle distribution and formulation heterogeneity. The increased data volume requires more advanced image processing and chemometrics, but the resulting information can provide a deeper understanding of formulation structure.

NIR Application Summary

Application	Typical quality attribute	Role of NIR
Raw material ID	Identity	Rapid classification
Moisture analysis	Water content	Quantitative prediction
Granulation	Moisture/process state	In-process monitoring
Drying	Residual moisture	Endpoint support
Blend monitoring	Uniformity	Continuous assessment
Tablets	Assay/content uniformity	Non-destructive prediction
Compression	Physical/chemical attributes	Process monitoring
Coating	Coating progression	Endpoint/process control
Continuous manufacturing	Material quality and state	PAT measurement

RAMAN AND NIR IN PROCESS ANALYTICAL TECHNOLOGY AND REAL-TIME RELEASE

Process Analytical Technology is built around the idea that timely measurements of process and material attributes can improve process understanding and control. The FDA PAT framework encouraged pharmaceutical manufacturers to consider analytical measurements as part of an integrated manufacturing strategy rather than limiting testing to the final product. Raman and NIR are particularly compatible with PAT because they can acquire measurements rapidly and can be connected to process equipment through fiber-optic probes. [2,12]

Off-Line, At-Line, On-Line and In-Line Measurements

Mode	Description	Example
Off-line	Sample is removed and tested away from the process	Laboratory Raman analysis of tablets
At-line	Measurement is performed close to the process with limited sample movement	NIR testing near a manufacturing line
On-line	Sample is diverted or presented to analyzer during operation	Flow-through process measurement
In-line	Measurement occurs directly within the process stream	Probe installed in a blender or dryer

The distinction matters because the closer the measurement is to the process, the more attention must be given to mechanical integration, cleaning, probe fouling, window integrity, data transfer, process safety and maintenance. A laboratory method may be analytically excellent but unsuitable for direct process installation. PAT implementation therefore requires engineering and process knowledge in addition to spectroscopy.

Real-Time Release Testing

Real-time release testing (RTRT) aims to use process and analytical information to support a decision about product quality at or near the time of manufacture. Spectroscopy can contribute to such a strategy when the method is scientifically justified, validated for its intended use and integrated with a control strategy. RTRT should not be interpreted as simply replacing every laboratory test with a spectrum. It requires demonstrated understanding of material attributes, process relationships, model performance and decision uncertainty.

Quality by Design

Quality by Design emphasizes systematic understanding of how formulation and process variables affect product quality. Raman and NIR measurements can support QbD by providing information on material attributes and process trajectories. During development, spectral measurements may help identify process

variables associated with changes in blend uniformity, moisture, solid state or composition. During routine manufacture, the same measurements may become part of process monitoring.

Continuous Manufacturing and Data Density

Continuous processes generate a large amount of material over time rather than producing discrete batches in the same manner as traditional operations. Spectroscopic instruments can provide frequent measurements, producing a dense time series. This can support material traceability and detection of disturbances. However, more data does not automatically mean better control. Data management, model maintenance, synchronization with process events and scientifically justified alarm limits become increasingly important.

METHOD DEVELOPMENT, VALIDATION AND REGULATORY CONSIDERATIONS

Analytical method development for Raman and NIR should begin with a clear statement of intended use. The same instrument can be used for identification, assay, moisture prediction or process monitoring, but each purpose creates different performance requirements. The method should be developed around the quality decision rather than around the convenience of obtaining a statistically attractive model.

Defining the Analytical Target

The analytical target may be identity, concentration, moisture, solid form, uniformity or another critical quality attribute. The target should be measurable by a suitable reference method when calibration is quantitative. The expected range and sources of variability should be established before collecting calibration data.

Reference Methods

Quantitative spectroscopic models generally require reference measurements. The reference method must itself be appropriate, because systematic error in the reference can be transferred into the spectroscopic model. Reference samples should cover the intended range and include natural variation. Artificially prepared mixtures can be useful during development but may not reproduce all sources of manufacturing variability.

Validation Characteristics

ICH Q2(R2) states that analytical procedure validation is intended to demonstrate suitability for the intended purpose. Depending on the analytical use, characteristics such as specificity/selectivity, accuracy, precision and reportable range are relevant. Robustness should be considered during development. [5] For spectroscopic methods, validation should additionally address model applicability, spectral preprocessing, sample presentation and the handling of out-of-model samples.

Validation element	Relevance to Raman/NIR
Specificity/selectivity	Ability to distinguish target material or attribute from interfering spectral variation
Accuracy	Agreement between predicted and accepted reference values
Precision	Repeatability and intermediate precision under defined conditions
Range	Interval over which the model provides reliable performance
Robustness	Resistance to relevant changes in measurement and sample conditions
Model applicability	Ability to identify samples outside the calibration domain
System suitability	Routine evidence that the instrument/model is functioning adequately

Calibration Set Design

Calibration design is one of the most important determinants of model quality. A calibration set should include representative lots, suppliers, strengths, excipient variability, manufacturing conditions and physical states expected during routine use. The range should be wide enough to support the intended application but should not contain unrealistic combinations that could distort the relationship between spectral and reference data.

Independent Test Sets

An independent validation set provides a more credible estimate of predictive performance than repeated testing of the same calibration samples. The test set should represent the intended future population and should preferably include sources of variation not duplicated exactly from the calibration set. If a model performs well only on samples that closely resemble the calibration set, its practical value is limited.

Outliers and Model Domain

An unusual spectrum may represent an instrument problem, sample contamination, an unexpected formulation, a new supplier, a physical change or genuine product failure. Automatically deleting unusual observations can conceal important information. A scientifically controlled procedure should distinguish analytical errors from legitimate new variation and define when model maintenance or investigation is required.

Regulatory Perspective

Regulatory acceptance depends on the intended use, scientific justification and evidence demonstrating that the method is fit for purpose. The ICH Q2(R2) guideline provides a general framework for validation, while PAT-oriented applications require additional understanding of process relationships and control strategies. [5] Pharmaceutical NIR has also been discussed in the context of pharmacopoeial approaches and method validation, with literature emphasizing that statistical calibration alone is insufficient without appropriate validation. [4]

Data Integrity and Software Control

Spectroscopic methods depend heavily on software. Raw spectra, preprocessing settings, calibration versions, prediction results and audit information should be managed in accordance with applicable data-integrity expectations. Changes to preprocessing or model coefficients can change reported results and should therefore be controlled. User access, backup, version control and documentation are important components of a computerized analytical system.

COMPARATIVE EVALUATION OF RAMAN AND NIR SPECTROSCOPY

Raman and NIR spectroscopy are complementary vibrational methods. Both can provide rapid, non-destructive analysis and can be adapted for process monitoring, but they differ in their physical basis and practical response to pharmaceutical matrices. Choosing between them should therefore depend on the analytical target, sample characteristics, expected interferences and process requirements.

Parameter	Raman spectroscopy	NIR spectroscopy
Physical principle	Inelastic scattering	Absorption
Spectral appearance	Usually sharper characteristic bands	Broad overlapping bands
Chemometrics	Useful for complex quantitative work	Frequently central to quantitative applications

Water interference	Often relatively limited compared with NIR	Strong spectral contribution from water
Fluorescence	Potential major interference	Generally not a Raman-type fluorescence issue
Solid-state information	Strong potential, including polymorphism	Can provide physical information but may be less structurally specific
Measurement through packaging	Possible with suitable materials	Possible with suitable materials and optical path
Bulk analysis	Transmission Raman can probe bulk	Transmittance/reflectance depend on sample properties
Process probes	Available	Widely used
Typical strengths	Molecular fingerprinting and solid-state sensitivity	Rapid multicomponent analysis and moisture/process monitoring

A practical strategy may involve using both techniques at different stages. Raman may be selected for identity and solid-state characterization where sharp molecular information is valuable, while NIR may be selected for moisture, blending and high-frequency process measurements. In some development programs, orthogonal spectroscopic information can be useful for investigating complex formulations. The decision should remain evidence-based rather than assuming that one method is universally superior.

ADVANTAGES, LIMITATIONS AND PRACTICAL IMPLEMENTATION

Advantages

- Rapid spectral acquisition can reduce analytical turnaround time.
- Measurements can often be performed without extensive sample preparation.
- Many applications are non-destructive, allowing the sample to be retained.
- Multiple chemical components may be assessed from a single spectrum.
- Fiber-optic probes can support at-line, on-line and in-line measurements.
- Spectroscopy can generate dense process data suitable for PAT.
- Reduced solvent use may support more resource-efficient analytical workflows.
- Imaging configurations can provide spatial information in addition to spectral information.

Limitations

- Spectral interference and overlapping signals can complicate interpretation.
- Raman measurements may be affected by fluorescence and laser-induced heating.
- NIR spectra are broad and often require sophisticated chemometric modelling.
- Calibration models may not remain valid when material or process variability changes.
- Sampling problems can produce representative errors even when the instrument is precise.
- Instrument performance and probe condition can influence routine measurements.
- High-quality model development requires appropriate reference data and statistical expertise.
- Initial implementation may require investment in instruments, software, process integration and training.

Practical Implementation Strategy

Successful implementation should begin with a well-defined analytical problem. A feasibility study can establish whether useful spectral differences exist and whether the measurement is compatible with the manufacturing environment. This should be followed by representative data collection, reference testing, model development and validation. Pilot implementation should then examine routine factors such as operator variability, cleaning, probe placement, environmental conditions and instrument drift.

Training is equally important. Personnel need to understand not only how to collect a spectrum but also what the model result means, when a result should be accepted, and when an unusual spectrum should trigger investigation. Spectroscopic systems can appear simple to operate while hiding complex statistical assumptions. Good procedures therefore emphasize both instrument operation and analytical judgement.

Common Failure Modes and Preventive Measures

Failure mode	Likely cause	Preventive approach
Unstable predictions	Instrument or sampling variation	Routine checks and representative sampling
False classification	Incomplete reference library	Expand library with realistic variation
Poor quantitative accuracy	Weak or biased calibration set	Improve reference design and validation
Drift over time	Instrument/material changes	Lifecycle monitoring and model update procedure
Fluorescent Raman spectrum	Sample or wavelength effect	Alternative excitation and controlled baseline strategy
NIR model affected by particle size	Physical scattering variation	Representative calibration and scatter correction
Process endpoint inconsistent	Poor sampling location or definition	Link endpoint to quality attribute and process understanding

EMERGING TRENDS AND FUTURE SCOPE

The future of Raman and NIR spectroscopy in pharmaceutical quality control is likely to involve closer integration of optical measurement, chemometrics, process engineering and digital manufacturing. Instrument miniaturization, improved detectors, automated sampling and advanced data analysis are making spectroscopic measurements more accessible outside conventional laboratories. At the same time, the increasing use of continuous manufacturing creates a need for reliable real-time information.

Portable and Handheld Spectroscopy

Portable Raman and NIR instruments can extend testing closer to warehouses, manufacturing areas and field locations. Their value is greatest when the measurement question is well defined and the device has been qualified for the intended environment. Portability does not remove the need for calibration, library control or data integrity.

Low-Frequency Raman

Low-frequency Raman provides access to vibrational information associated with lattice and intermolecular motions. This creates opportunities for improved solid-state characterization, including discrimination of crystalline forms. Recent reviews identify low-frequency Raman as an active area of pharmaceutical analysis. [16]

Raman and NIR Imaging

Imaging adds a spatial dimension to spectroscopy and can reveal component distribution that a single-point measurement cannot show. As detector arrays, scanning systems and computational methods improve, imaging may become increasingly useful for formulation development and investigation of heterogeneity.

Machine Learning and Advanced Chemometrics

Modern data science methods can analyze complex spectral datasets and may improve classification or nonlinear prediction in selected applications. However, more complex algorithms do not automatically produce better analytical methods. Interpretability, representative training data, overfitting control, external validation and lifecycle monitoring remain essential. For regulated pharmaceutical applications, model transparency and traceability are especially important.

Cloud and Networked Analytical Systems

Networked instruments can support centralized model management, monitoring and data review across multiple manufacturing locations. Such systems could facilitate standardized calibration transfer and performance tracking, but cybersecurity, data integrity, access control and validation of computerized systems must be addressed.

Combination of Raman and NIR

Because Raman and NIR respond differently to molecular and physical characteristics, combined approaches may provide complementary information. Data fusion can be performed at different levels, from combining predicted attributes to integrating spectral variables into multivariate models. The scientific justification should focus on whether the combined information improves the intended quality decision.

Role in Green Analytical Chemistry

The potential to reduce solvents, sample preparation and waste makes Raman and NIR relevant to greener analytical strategies. Their environmental advantage should nevertheless be evaluated across the complete system, including instrument energy use, consumables, calibration materials and maintenance. A rapid method is not automatically a green method, but nondestructive spectroscopy can reduce several resource-intensive laboratory steps.

DISCUSSION

The literature reviewed in this thesis shows that Raman and NIR spectroscopy have moved beyond experimental demonstrations and have become established tools for selected pharmaceutical analytical problems. Their strongest contribution is not that they replace every conventional laboratory method, but that they provide a different form of information: rapid, multivariate and potentially available at the point where the process is occurring.

NIR has particular strength in applications involving moisture, multicomponent analysis and process monitoring. Its broad spectral bands are a disadvantage for direct structural interpretation but become useful when the spectral response is interpreted statistically. This is why calibration design and chemometrics are inseparable from practical NIR quality control. The literature repeatedly emphasizes that representative samples and appropriate validation are essential for reliable pharmaceutical NIR methods. [1,3,4]

Raman provides a different analytical profile. The bands are often sharper and can offer useful molecular fingerprints and solid-state information. This can be advantageous for raw-material identification, polymorph discrimination and formulation characterization. Transmission Raman expands the technique from surface-

focused measurements toward bulk analysis of intact dosage forms, while low-frequency Raman adds information relevant to crystal packing and long-range order. [16,17]

For process monitoring, the two methods share several advantages. Both can be coupled with fiber-optic probes and can generate measurements at high frequency. This makes them suitable candidates for PAT. The 2011 review by De Beer and colleagues highlighted their use for real-time pharmaceutical process monitoring, including blending and other manufacturing stages. [2] More recent reviews continue to describe NIR and Raman as important spectroscopic technologies for modern pharmaceutical analysis and quality control. [6,10,11]

The main challenge is not the acquisition of spectra but the translation of spectra into reliable decisions. A chemometric model can be statistically impressive and still be unsuitable if the calibration set is biased, if the reference method is unreliable, or if routine samples fall outside the calibration domain. Spectroscopic methods should therefore be developed as complete analytical systems. Sampling, reference testing, preprocessing, model construction, validation, software, instrument performance and decision rules must all be considered.

Another important issue is the distinction between correlation and causation. A model may predict tablet hardness because hardness changes scattering, while the developer may mistakenly interpret the result as direct chemical measurement. Similar effects can occur when moisture, particle size or density is correlated with API concentration. Robust study designs should deliberately challenge these correlations and establish whether the model measures the intended attribute or an accidental surrogate.

Regulatory science is also evolving. ICH Q2(R2) provides a modern framework for analytical procedure validation and emphasizes suitability for intended purpose. [5] Spectroscopic applications add the need for model lifecycle management and appropriate control of calibration updates. This is particularly important when a model is used for routine release or process control, because changes in suppliers, equipment, formulation or manufacturing scale can change the spectral population.

Overall, Raman and NIR spectroscopy should be viewed as complementary technologies within a broader analytical control strategy. The most successful implementations are likely to be those in which the spectroscopic method is connected to a clearly defined quality attribute, supported by representative data, validated against an appropriate reference and integrated with process understanding. This approach is consistent with the broader direction of pharmaceutical manufacturing toward science-based control, QbD and increased use of real-time information.

CONCLUSION AND RECOMMENDATIONS

Raman and near-infrared spectroscopy have significant applications in pharmaceutical quality control because they can provide rapid, non-destructive and information-rich measurements with limited sample preparation. Their applications include raw-material identification, assay, content uniformity, moisture determination, blend monitoring, granulation and drying control, tablet and coating assessment, solid-state characterization, counterfeit screening and process monitoring.

Raman spectroscopy is particularly valuable when molecular fingerprinting, solid-state information or transmission measurements are desired. NIR spectroscopy is especially useful for rapid multicomponent measurements, moisture analysis and process monitoring. The techniques are complementary because their different physical principles produce different patterns of analytical sensitivity.

The most important practical lesson is that successful spectroscopy depends on more than instrument selection. Representative sampling, high-quality reference data, appropriate chemometric methods, independent validation, instrument qualification, software control and lifecycle management are necessary for reliable routine use. ICH Q2(R2) provides a general framework for analytical validation, while PAT and QbD concepts provide a broader framework for integrating spectroscopic measurements with manufacturing control. [5]

Future development is expected to focus on portable instruments, low-frequency Raman, hyperspectral imaging, improved fiber-optic systems, advanced chemometrics, data fusion, continuous manufacturing and real-time release strategies. As these technologies develop, the emphasis should remain on scientific validity and fitness for purpose rather than on replacing established analytical procedures simply because a new technology is available.

Recommendations

- Select Raman or NIR only after defining the exact quality attribute and intended decision.
- Use representative calibration and validation samples that reflect realistic manufacturing variability.
- Treat sampling strategy as an integral part of method development.
- Use validated reference procedures for quantitative model development.
- Establish documented procedures for out-of-model and atypical spectra.
- Monitor model and instrument performance throughout the analytical lifecycle.
- Consider Raman and NIR as complementary tools rather than universally interchangeable methods.
- Integrate spectroscopy with PAT, QbD and process understanding where appropriate.
- Maintain appropriate training, software control and data-integrity procedures.
- Use conventional confirmatory methods when required by the intended application or regulatory framework.

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