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Medicinal and Analytical Chemistry International Journal
ISSN: 2639-2534

Pharmaceutical Applications and Importance of Near Infrared Spectroscopy

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Review Article

Volume 4 Issue 1

Received Date: February 26, 2020

Published Date: April 10, 2020

DOI: 10.23880/macij-16000155

Abstract

Innovative instrumentation, highlighted by portable and imaging instruments, chemometrics data multivariate processing, and new and valuable applications are presented and discussed. Because of these advances, this mature analytical technique is continually experiencing renewed interest. The drawbacks and misuses of the technique and its supporting mathematical tools are also addressed. The principal achievements in the field are shown in a critical manner, in order to understand why the technique has found intensive application in the most diverse and modern areas of analytical importance during the last ten years. This paper intends to review the basic theory of Near Infrared (NIR) Spectroscopy and its applications in the field of Analytical Science. It is addressed to the reader who does not have a profound knowledge of vibrational spectroscopy but wants to be introduced to the analytical potentialities of this fascinating technique and, at same time, be conscious of its limitations. Essential theory background, an outline of modern instrument design, practical aspects, and applications in a number of different fields are presented. Near-infrared spectroscopy (NIRS) is a relatively new and increasingly widespread brain imaging technique, particularly suitable for use with young infants. The technique employs near-infrared light to assess the concentration changes of oxygenated and deoxygenated hemoglobin, accompanying local brain activity. The basic physical, physiological, and neural principles underlying the use of NIRS and some of the existing developmental studies are reviewed. Issues concerning technological improvements, parameter optimization, possible experimental designs, and data analysis techniques are also discussed and illustrated.

Keywords: Developmental Cognitive Neuroscience; Functional Brain Imaging; Hemodynamic Response; Near-Infrared Spectroscopy; Optical Tomography; Optical Topography

Abbreviations: NIR: Near Infrared; NIRS: Near-Infrared Spectroscopy; PAT: Process Analytical Technology; GMP: Good Manufacturing Practice; RTR: Real Time Release; MAPP: Manual of Policies and Procedures; CMC: Chemistry, Manufacturing, and Controls; OPS: Office of the Pharmaceutical Science; MIR: Mid-Infrared; QbD: Quality by Design; IPC: Instrument Performance Certification; IR: Infrared.

Introduction

Near-infrared (NIR) spectroscopy is a highly flexible form of analysis, which can be applied to a broad range of research and industrial process applications. Long a staple technology in remote sensing, NIR spectroscopy has become popular within industrial markets as a cost-effective tool for measuring materials to optimize processes and manage

costs. NIR spectroscopy is referred to as a new technology, it was discovered in 1800 when Herschel found that dispersion of electromagnetic waves beyond the visible range of the spectrum could be observed by using a series of thermometers with blackened bulb [1]. Near-infrared spectroscopy measures the absorption of electromagnetic radiation including wavelengths from 750 to 2500nm. The absorptions measured by NIR spectroscopy correspond mostly to overtones and combinations of vibrational modes involving C-H, O-H, and N-H chemical bonds [2]. Although near-infrared (NIR) spectroscopy is not a particularly sensitive technique, it can be implemented with little or no sample preparation and thus is well suited to applications such as process monitoring, materials science, and medical uses. We asked a panel of experts to comment on important current applications of NIR, as well as emerging new areas of application and the challenges involved in those newer applications. Process Analytical Technology Nowadays, conventional pharmaceutical manufacturing is generally accomplished using batch processing with laboratory testing conducted on randomly collected samples to evaluate their conformity. The latter approach slows down the batch release step as most of those conformity tests are carried out on end-product samples. Moreover, most manufacturing processes are performed with frozen process parameters, any changes in the manufacturing procedure requiring a new regulatory submission. Based on the previous considerations, FDA proposed a new concept: Process Analytical Technology (PAT) which can be defined as "a system for designing, analyzing, and controlling manufacturing by measuring the critical quality & performance attributes for raw and in process materials ensuring the final product, confirming the concept of the pharmaceutical Good Manufacturing Practice (GMP) of the 21st century [3-7]. To ensure the final product quality, PAT requires adequate process analyzers. These analyzers should be used first to identify the processing steps impacting the most on the targeted product performance. Next, the real time monitoring of the identified critical processing steps should be achieved with analytical method developed on the selected process analyzers. Based on the collected data, the product critical quality attributes can be monitored and if necessary adjusted in real time by means of feed-back and feed-forward control loops enabling to keep the manufacturing within the defined product specifications. Depending on the proximity between the manufacturing line and the process analyzers, off-line, at-line, on-line and in-line measurements can be performed. Off-line defines a measurement where the sample is removed, isolated from, and analyzed away from the process stream. The concept is the same for the at-line measurement except that the analysis is performed in close proximity to the process stream. On-line characterizes a measurement where the sample is diverted from the manufacturing process, and may be returned to the process stream. If the manufacturing line and process analyzers allow it, in- line measurements are the shortest and ideal way to monitor the insight of a process as the sample is not removed or diverted from the process stream. This measurement can be invasive or non-invasive. The data gathered during the production will provide a better process understanding and may also enable the Real Time Release (RTR) of the pharmaceutical batches. Facing the requirements of the PAT tools, there is a need for analytical techniques being able to acquire a large amount of data within seconds during all the critical steps of a pharmaceutical manufacturing process. The advantages of vibrational spectroscopic techniques such as NIR and Raman spectroscopy, which will be discussed in the next sections, match the requirements of the PAT framework. Several comprehensive reviews have summarized studies reporting the capabilities of NIR spectroscopy in the area of meat quality [8-10]. However, this technology still has some limitations and online applications under industrial environments remain challenging.

Together with PAT, there is also an increasing demand from the regulatory authorities towards the pharmaceutical industries to gain a comprehensive understanding of their processes together with an accurate estimation of their robustness and reliability. Instead of providing solutions to meet these demands and requirements, authorities have published guidelines establishing the philosophy to achieve these expectations. In the ICH Q8 (R2) guideline on pharmaceutical development, the emphasis is put on the "Quality by Design" concept, stating that the quality should not be tested into products, but should be built in. The Design Space concept is also introduced in this guideline, which is "the multidimensional combination and interaction of input variables (e.g., materials attributes) and process parameters that have been demonstrated to provide assurance of quality". Furthermore, ICH indicates that as long as the process and formulation parameters are kept within the defined Design Space, no regulatory post approval change is needed. Furthermore, the Design Space of a process also guarantees its reliability and robustness, supporting the quality risk management system. Facing the challenges and expectations of the ICH Q8 (R2) guideline on the pharmaceutical development, the process analyzers as described in the PAT concept can be advantageously integrated in a general Quality by Design quality system to provide reliable real time information helping to define the process design space. Accordingly, this combination of real time analysis together with advanced process understanding and improved quality risk management are clearly promoting factors to achieve consistent product performance as per ICH Q10 guideline. Besides, in addition of being highly encouraged, the key concepts and recommendations appearing in the ICH Q8 (R2), Q9 and Q10 guidance to industry are now becoming more and more mandatory: this can be read in the recent Manual

of Policies and Procedures (MAPP) 5016.1 document for the chemistry, manufacturing, and controls (CMC) reviewers in the Office of the Pharmaceutical Science (OPS). The document is effective since 2nd August of this year and clearly highlights the use of PAT and QbD as follows: "Reviewers should determine whether an application includes sufficient enhanced knowledge that demonstrates the applicant's understanding of materials attributes, manufacturing processes, and controls for product quality to support the proposed flexible regulatory approaches. In-process tests in lieu of end product testing, including real time release testing approaches (e.g., "PAT-A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance," September 2004)".

Near-infrared spectroscopy (NIRS) works on the principle of absorption of radiation by matter. Not only does the versatile technique allow the parallel identification of substances (active agents, excipients, contaminants), it is also suited to monitor processes such as blending, granulation, and drying.

NIRS-Interaction of Light and Matter

Molecular vibrations area unit elicited within the near-infrared region of the magnetic spectrum (800–2500nm)-i.e., from the top of the visible to the mid-infrared (MIR) vary. The most absorption bands of the purposeful teams of chemical substances area unit set within the MIR vary and area unit terribly sturdy. The absorption bands of the harmonics, and also the combination of the basic molecular vibrations, however, area unit within the NIR spectral region. They considerably weaker and modify direct mensuration while not sample preparation, whereas at an equivalent time giving deep insights into the chemical and physical properties of the sample. The strongest overtone absorptions within the NIR vary area unit displayed by compounds with Buckeye State, CH, NH, and SH bonds.

Because the NIR spectrum represents the results of varied overlapping absorption bands, it's ordinarily evaluated with variable chemometric strategies. NIRS is economical and quick facultative qualitative and quantitative analyses that area unit noninvasive and non-destructive. NIRS is an important analysis technique that may be used on the complete production chain-from incoming materials to process to the standard management of finished merchandise (Figure 1). NIRS meets the necessities of diverse international pharmacopoeias, e.g., USP, Ph. Eur., and JP.

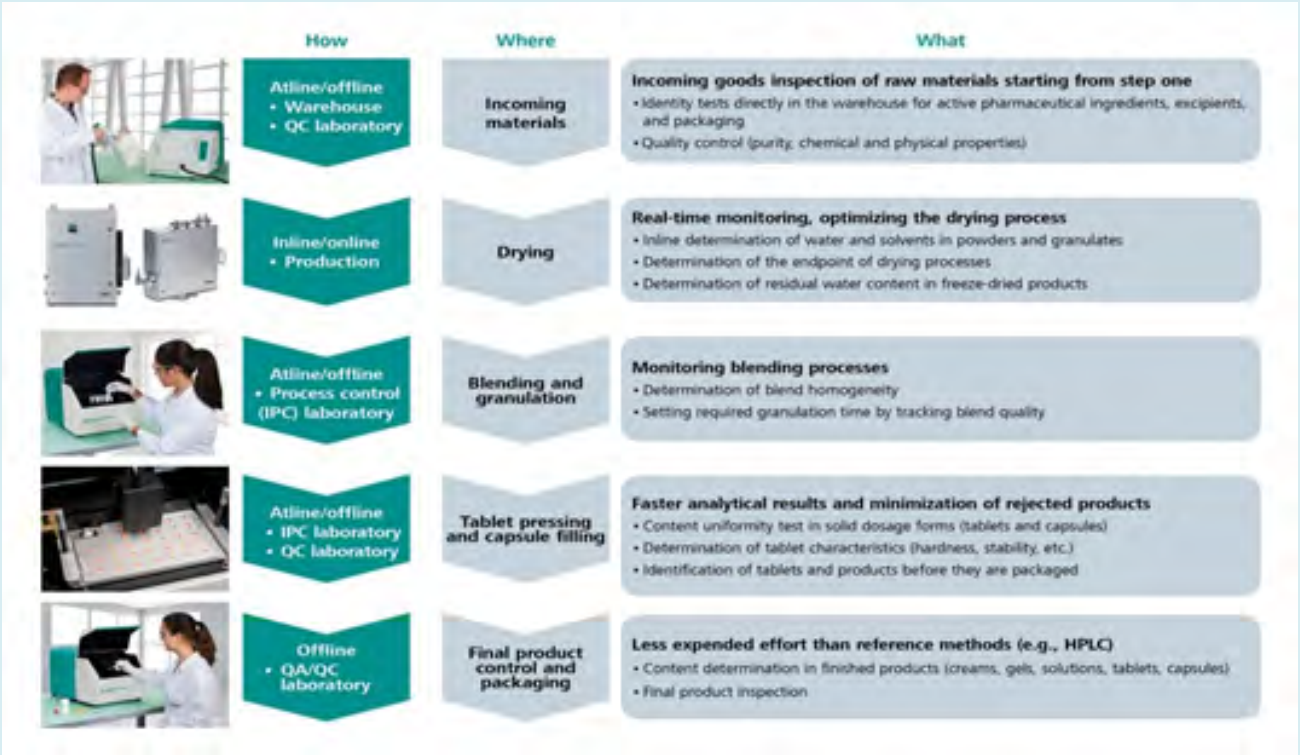

Figure 1: Applications of NIRS along the production chain.

Analyses of Diverse Matrices

Near-infrared spectroscopy requires no sample preparation and can handle any sample matrix, whether it is powders or granulates, tablets or capsules, creams or gels, solutions or suspensions, polymer films, or freeze-dried samples.

Screening through Packaged Materials

NIRS can even perform determinations on contents sealed in transparent packaging such as glass and films. This is particularly appealing for incoming goods inspections and packaged end products. Handling is so easy that NIRS can be used directly in pharmacies and customs offices.

Nondestructive Analysis

NIRS has long been one of the most important and versatile analytical techniques in the pharmaceutical industry-and not just because everybody in the pharma industry is talking about process analytical technologies (PAT) and Quality by Design (QbD). The decisive benefit of NIRS is the possibility of obtaining reliable analysis results in just seconds without altering the material under investigation and without any sample preparation or reagents whatsoever.

PAT and Qbd-in Search of the Best of All Methods

Drug producing is subject to sturdy changes. The FDA's explicit goal is to chop development time for brand new medicine whereas at a similar time considerably rising quality. This demand will solely be consummated with analytical techniques that monitor the complete method-from incoming raw materials to the ultimate product. To attain that, excellent PAT sensors square measure required that alter "live" trailing of the producing method. NIRS is that the technique that produces this potential. Associate in nursing inline sensing element monitors product quality in real time. This prevents charges associated with rejected product and reduces overall prices. An example: granulation and drying.

A key producing method within the pharmaceutical trade is that the granulation and drying method for powders that proceeds pill producing. This method makes it potential to press powders into tablets within the 1st place. NIRS is that the technique of selection for decisive the reaction end {point| termination| terminus |end} once press ability is at the best point. Probes within the drier or granulator build it potential to trace the method in real time. That reduces the method period and therefore will increase the drying and granulation capability of the system. At a similar time, it minimizes the deviation of the specified set point values. Figure 2 shows an activity model for water determination that correlates NIRS to Karl Fischer volumetric analysis that is that the reference technique. The progressive diminution of the water content throughout the granulation method, measured by period NIRS, is seen within the Figure 3.

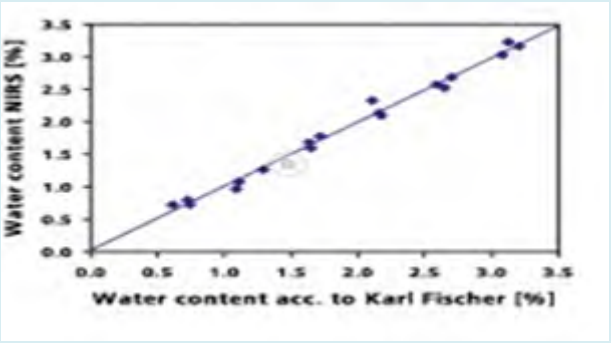

Figure 2: Calibration model for quantitative determination of water content in powders. Karl Fischer titration is used as reference method.

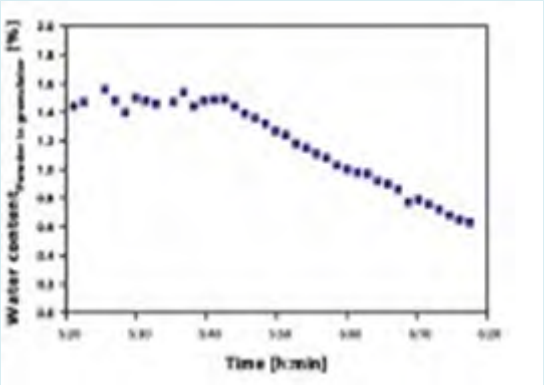

Figure 3: Reduction of water content in a pharmaceutical powder over time.

Rapid and nondestructive NIR analysis makes it possible to determine the optimal moment for further processing in real time. The sensor is installed directly in the granulator. In accordance with international pharmacopoeias as a secondary test method, NIRS is recommended in all of the key pharmacopoeias – from the European (Ph. Eur. 2.2.40) to the American (USP<1119>) to the Japanese pharmacopoeia. Metrohm NIR Systems offers instruments that meet the standards for wavelength precision, reproducibility, and photometric noise. Numerous reference standards and the user-friendly software make it easy to verify the instrument's compliance with requirements specified in the pharmacopoeias. The pharmaceutical version of the Vision software is fully validated and compliant with 21 CFR Part 11. Metrohm NIR Systems also offers complete IQ/OQ documentation and instrument performance certification

(IPC). Documented parameters guarantee that the instrument performs properly.

Current State of Near IR Spectroscopy Applied to Pharmaceutical Analysis: Various techniques of IR spectroscopy are considered from the standpoint of their application in pharmaceutical analysis. It is demonstrated that attenuated total reflectance in the mid-IR range and near-IR spectroscopy are promising techniques for pharmaceutical analysis.

Infrared Spectroscopy for Protein Analysis in the Pharmaceutical Industry: The interaction of infrared radiation with molecules can be analyzed using a technique called the infrared (IR) spectroscopy. Although, the most popular analysis technique is absorption spectroscopy, reflection and emission can also be used. In IR spectroscopy, infrared light is passed through a sample, following which the absorption of light at each frequency is measured. Thus, an infrared spectrum with peaks denoting the absorbed radiation frequency is obtained.

IR spectroscopy uses samples that can be gases, liquids or solids. Unknown chemicals in these samples can be analyzed and identified by IR spectroscopy, making it advantageous for protein analysis in the pharmaceutical industry (Figure 4).

Figure 4: Infrared Spectroscopy for Protein Analysis.

As IR spectroscopy is a simple technique and also provides a cost-effective approach to study protein at any buffer conditions in aqueous media, this technique proves to be beneficial for protein analysis. Thus the technique is now a powerful tool for formulation optimization, stability studies and quality control of protein drug products in the pharmaceutical industry. The formation of fibrils or aggregates can be monitored in real time using IR spectroscopy. In addition, using this technique, the structural effects of proteins can also be isolated while the adhere.

Confocheck FT-IR Spectrometer

CONFOCHECK is a Fourier transform infrared spectrometer system for protein analysis the protein spectrum is used to determine concentration confocheck is used to dertmine the concentration of molecular substance dissolved in water Confocheck consists of two FT-IR sample cells.

Aquaspace Cells: It is used to determine the proteins in aqueous solutions and they are some typical applications like conformational stability and concentration of secondary structure components.

BIOATR II: It is used for the aggregation and precipitation of water soluble protein and membrane.

Applications of Near IR Spectroscopy

Identification of functional group and structure education: The IR region is divided into regions they are mentioned as below

- Group frequency region
- Finger print region

The group frequency region is based upon the corresponding peaks. Based upon this phenomenon the functional group can be determined.

Identification of substances: The main objective of IR spectroscopy is to determine whether the given sample of an organic substance is identical with another substances or not. For example, an IR spectrum of benzaldehyde is observed as follows (Table 1).

Functional Group	Absorption Location(cm-1)	Absorption Intensity
Alkane (C–H)	2,850-2,975	Medium to strong
Alcohol (O–H)	3,400-3,700	Strong, broad
Alkene (C=C) (C=C–H)	1,640-1,680	Weak to medium
	3,020-3,100	Medium
Alkyne (C≡C) (C≡C–H)	2,100-2,250	Medium
	3,300	Strong
Nitrile (C≡N)	2,200-2,250	Medium

Aromatics	1,650-2,000	Weak
Amines(N–H)	3,300-3,350	Medium
Carbonyls (C=O)		Strong
Aldehyde (CHO)	1,720-1,740	
Ketone (RCOR)	1,715	
Ester (RCOOR)	1,735-1,750	
Acid (RCOOH)	1,700-1,725	

Table 1: IR Absorptions of common functional groups.

No other compound then benzaldehyde produces same IR spectra as shown above.

Studying the progress of the reaction: The absorption band is determined based upon the appearance and characteristic properties and reaction procedure.

Detection of impurities: The impurities can be detected by the IR spectrum of the test sample is compared with the standard compound.

Quantitative analysis: The base line technique is used determine the quantity of the substance. The quantity of the substance. The quantity of the substance let's assume it as x substance can be determine either in pure form or mixture of two or more compounds.

Conclusion

The application of NIR spectroscopy has known advantages (lower costs; rapid, in situ, and nondestructive analyses; multi-parameter estimation; and environmental friendliness). Although measurement costs are low using the NIR spectroscopy technique, instrument costs are high meaning practical applications may still be restricted by cost. Researchers and analysts are therefore looking for sensitive wavelengths in the NIR region representing characteristics of food products, allowing for development of simpler and more specialized instruments at a lower cost. If successful, the applications of NIR spectroscopy may become more widely used and popular in many meat industries. Next-generation NIR spectrometers may also have potential to be implemented in smartphones. As a consequence, future research for quality control applications in carcass, meat and meat products will likely focus on using NIR spectroscopy combined with other nondestructive technologies and the implementation of portable, low-cost next-generation NIR instruments.

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