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Near Infrared Spectroscopy: Applications in Pharmaceutical Industry

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Abstract

This work explores the comprehensive development of a near infrared (NIR) spectroscopic analytical technique for high-throughput applications for the determination of pharmaceutical raw materials and excipients in a pharmaceutical formulation. Advancements in the NIR spectrometry as quality and process control tool have been discussed. The applications include analyses of different types of samples, manufacturing and identification of active pharmaceutical ingredients based on specified experimental design. The samples were measured in diffusion or reflectance mode in a fourier-transform NIR spectrometer. Additionally, chemometric software was employed for quantitative interpretation of bands. The spectrometry can be utilized for identification of raw materials, their size, polymorphism and blend homogeneity.

Keywords: NIR, Polymorphism, Active pharmaceutical ingredients

1. Introduction

Over the years there has been lot of technological advancements and as such it was required by the industry, specifically the 'Pharmaceuticals' where in the Regulatory compliance

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requirements have increased tremendously. The variety and quantum of analysis in the Quality control department of the drug industry have increased recently and will keep on increasing in the future too.

Growing demands for 'proofs and evidences' forced by regulatory agencies on one side and fiscal sides on the other, the Quality control Laboratories are required to develop better analytical methodologies. This has been a challenging task to the drug industry as a whole.

The advancements in Near-Infrared Spectroscopy applications (NIR) has been a 'Blessing in disguise' for the drug manufacturing firms from as early as 1950s. Historically, the discovery of NIR region dates back to 1800 by Herschel, who segregated the Electromagnetic spectrum using a prism and observed an increase in temperature beyond the red region named Infra red region. The credit of using modern NIRs for analytical applications goes to Karl Norris a scientist from the U.S. Department of Agriculture. From then on, there has been a major breakthrough in the advancement and utilization of NIR technology in the drug industry as a Quality and Process control tool.

The NIR technology offers the Pharmaceutical industry, a faster, highly precise and cost effective methods which are required to be executed in a Current Good manufacturing practices (cGMP) environment. NIR Spectroscopy and imaging are fast and non-destructive methods used for physico-chemical information of multiple constituents of the sample matrix.

The NIR instruments are user friendly and are easy for operation and validations. It is also a proven and popular technique. It is rapid, accurate, non-destructive and can even analyze samples inside glass and plastic containers too.

These are thus being used for multiple applications in the Pharmaceutical industry. Therefore, NIR is been used in the warehouse to analyse incoming drug constituents, excipients and packing materials and in the manufacture shop floor for monitoring properties such as blend homogeny, moisture content and rate of dissolution.

NIR applications have further been officially authorized in the USP general chapter titled 'Near Infrared Spectrophotometry'. European agency for the evaluation of medicinal products (EMEA, London), the European Directorate for the Quality of Medicines, European Pharmacopeia (EDQM, France) and Pharmaceutical Analytical Sciences Group (PASG) have brought out these guidance documents. The lengthy Analytical methods can now be replaced with more faster and shorter NIR methods, with proper Analytical method validations and further approvals.

In NIR Spectroscopy, the diffusion or reflectance of the sample is measured in the wavelength region between 780 and 2500 nm (wavelength of light) / 12,820 - 4000 cm^{-1} (wave number) (Fig. 1).

A chemometric software is employed in the qualitative quantitative interpretation of overtone and combination bands formed by the excitation of covalent bonds such as CH, OH and NH. The wavelength region from mid Infrared upto the visible range are usually covered in NIR analysis. These are typically broad, allowing direct determination of highly absorbing and scattering samples such as turbid liquids or solids in transmittance or reflectance mode.

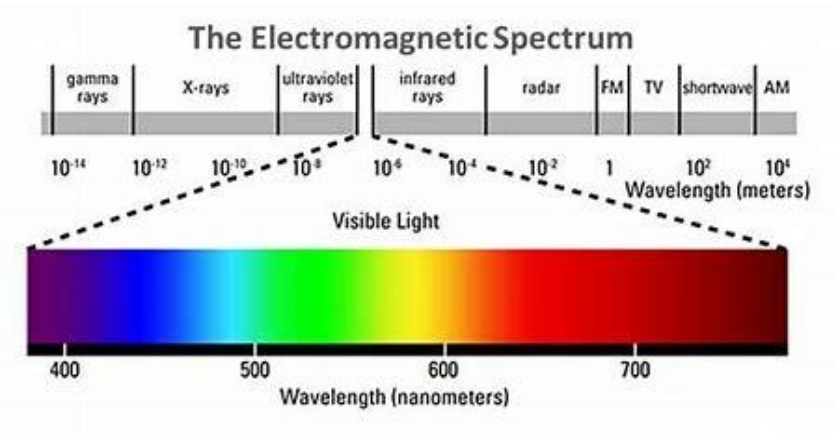


Figure 1: Electromagnetic spectrum

Figure 2: NIR Spectrometer

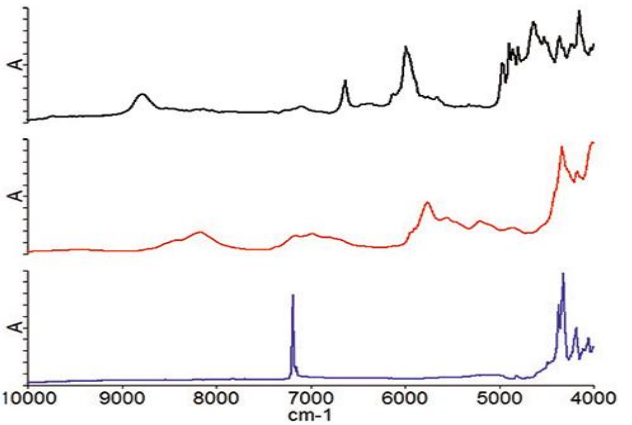


Figure 3: Typical NIR spectra of Pharmaceutical Raw materials: Diclofenac (black), Poloxamer (red), and Talc (blue).

NIR applications in the Pharmaceutical industry is for both Qualitative and quantitative analysis and is mainly used in the following areas –

- Identification, Process monitoring and control, Moisture control, Content uniformity, Coating thickness

- Sample types - Solids, Liquids, Tablets, Powders, Soft gels, Pastes, Films, Suspensions, Syrups etc.
- In manufacturing for – Blending and mixing, Reaction monitoring, Fermentation, Drying, Post- Tableting tests

NIR has been proven suitable for the following analysis –

- Raw material Identification
- Raw material Particle size
- Analysis of Parenteral Drugs (Lyophilized materials)
- Quantification of Active pharmaceutical ingredients in Tablets
- Blend Homogeneity
- Polymorph scanning
- Soft gel analysis
- Enzyme activity
- Detecting counterfeit drugs

NIR analysis can be used widely in Pharmaceutical, Chemical, Petrochemical, Food & beverage, Polymer and Agriculture industry.

NIR equipments on Blister packaging machines aides in detection of any faulty tablets. In addition, NIR is also suitable in detecting counterfeit drugs. The broad wavelength range of NIR, from 700 to 2500 nm, enables the analysis of pharmaceutical intermediates, additives and final products through packaging materials.

The non-destructive mode of examination of NIR is economical in manufacturing activities, since it minimizes the need for destructive testing and avoids the delay in obtaining analytical reports for Laboratory Analytical results. NIR applications in the Pharmaceutical industry also helps to reduce material inventory necessities, enhance throughput, and improve product consistency and quality.

1.1 NIR instrumentation

The NIR instrument typically consists of a light source, a monochromator, a sample holder or a sample presentation interface / sampling probe and a detector for Transmittance of reflectance measurements. Internal reference material is used for background correction.

For on-line or off-line measurements higher analyte sensitivity is required. The light source is usually a Tungsten halogen lamp. The mode of NIR measurements is dependent on the optical properties of the samples. For example the transparent materials are usually measured in Transmittance mode, the turbid liquids or semi-solids can be measured in diffuse transmittance or reflectance mode.

For performing the test of Identification by NIR 'Spectral library' is developed for each material and this is further dependant on the grades and particle size characteristics.

For proper sample analysis by NIR, the sample presentation is of utmost importance since scatter effects and stray light induced by packing materials (in the case of solid samples) may cause errors in the Spectra obtained. For monitoring the Process during manufacturing, Process Analyzers are used intended for real-time measurements.

Fiber Optic sampler – can perform Transflectance or Reflectance sampling e.g. Remote sampling – at-line, in-line, suitable for sampling of incoming Raw materials, Packing materials or In-process samples.

Blend uniformity analysis can be performed by the NIR probe inside the Blender when the Manufacturing process is ongoing. By scanning the sample, the progression of mixing and concentration of components can be measured and is very useful in the validation of the manufacturing processes.

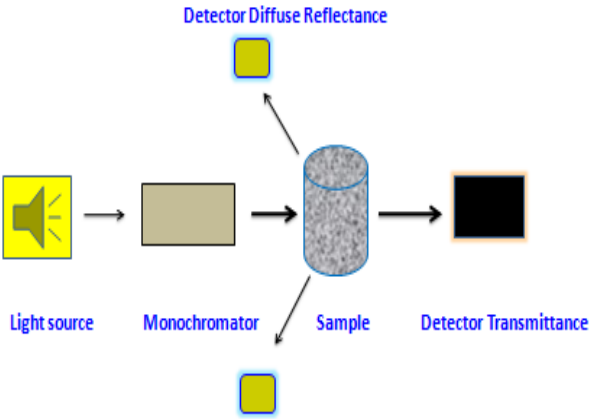
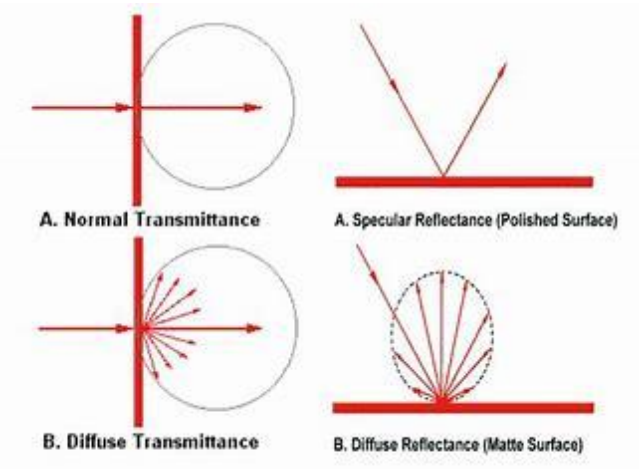


Figure 4: Basic NIR spectrometer configuration



1.2 Advantages of NIR Analysis

NIR analytical technology is beneficial since –

- It scans in a larger path-length → Can analyze more samples
- No Sample preparation required → is a non- destructive analysis
- Accurate and precise
- Analytical time is less

- No hazardous reagents are required for analysis
- Sampling techniques are Remote → can be scanned from the outside of the Pack

Many Pharmaceutical industries have effectively implemented NIR Spectrometers in their Quality Control Laboratories, Raw material sampling areas, Productions areas for the related applications.

Majority of the pharmacopeias have also added a chapter on NIR analysis and allows the organizations to use NIR methods with adequate method validation data.

Process Analytical Technology (PAT) by NIR in Pharmaceutical industry

The Process Analytical Technology (PAT) initiative driven by the United States Food and Drug Administration (US FDA) and some of the major Pharmaceutical organizations is a challenging approach intended for 'real time or parametric release' and Quality by design concepts. This gives an opportunity to move from the 'laboratory based testing' to continuous Quality assurance paradigm.

NIRs are placed at the receiving bay of the incoming Raw materials and are used for 'Identification' of each containers and the non-compliance is detected earlier than conventional sampling and analysis procedures. The technique thus is more cost effective and less time consuming.

These NIR technology is of immense importance in the analysis of Lyophilized / Sterile materials wherein the container / pack cannot be opened due to the chances of contamination and these can be analyzed 'without opening' the innermost pack. The quality of the materials thus is not compromised.

During the traditional manufacturing process, the optimal blending time is assessed during the process development / scale –up activities. NIR is used to determine the optimal mixing times with on-line sample analysis. This prevents incomplete/ inadequate or over-blending and assures uniformity and sustenance of the product Quality. NIR thus assists in elimination of Process errors,

in determination of the accurate end-points and enhancing of Process ruggedness.

NIR applications along with Bar code readers, Electronic weighing stations and Electronic Batch record documentation systems guarantees an excellent, successful and 'smart 'system for Pharmaceutical manufacturing processes.

With the ongoing continuous advancements in NIR hardware and software designs, added with the concepts of 'Quality by Design and Parametric releases', the NIR applications shall further penetrate into the various manufacturing and analytical procedures, for ensuring better compliances and enhanced productivity.

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